THE STATISTICAL ANALYSIS PLAN

Dual Antiplatelet Therapy For Shock Patients With Acute Myocardial Infarction

DAPT-SHOCK-AMI study (PRAGUE-23)

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The undersigned have reviewed the DAPT-SHOCK-AMI SAP and agree with its contents.

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Contents

Aim of the statistical analysis plan

This statistical analysis plan (SAP) aims to describe in detail the definitions and statistical methods to be implemented for the primary and secondary endpoint analyses in the Dual AntiPlatelet Therapy for SHOCK patients with Acute Myocardial Infarction (DAPT-SHOCK-AMI) study. Specifically, the plan aims to prospectively define the study populations and endpoints and outline the types of analyses and data presentations used. The actual version of SAP is based on the relevant sections of the DAPT-SHOCK-AMI study protocol, AMENDMENT 2, dated July 7, 2021.

Study design and data collection

Aim of the DAPT-SHOCK AMI study

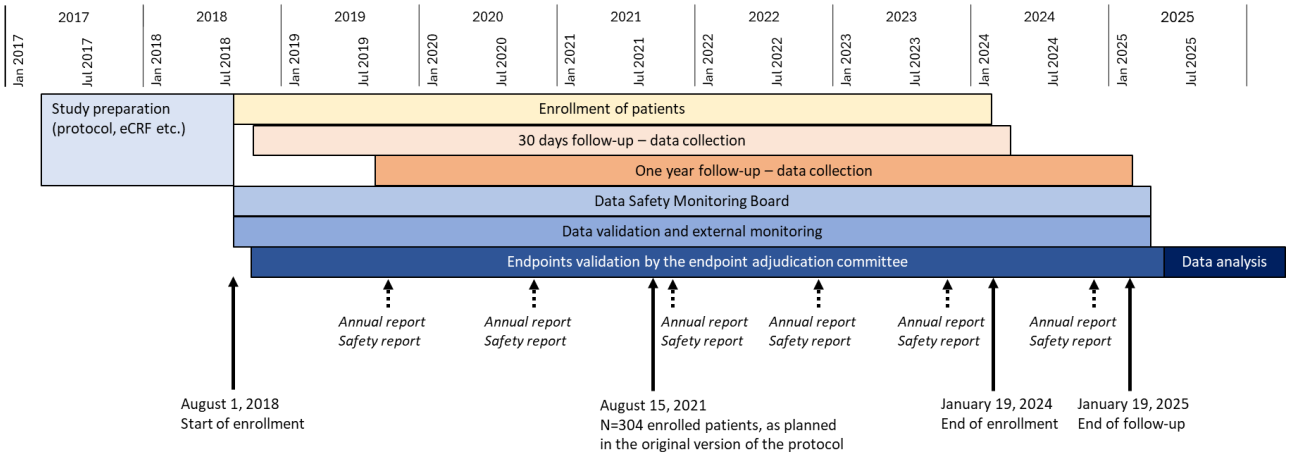
The DAPT-SHOCK AMI is a prospective, international, multicenter, randomized, double-blind controlled trial that compares the effects of parenteral cangrelor to the recommended treatment of crushed ticagrelor on i) periprocedural adenosine diphosphate (ADP) activated platelet aggregation and ii) the occurrence of major cardiovascular events in patients with acute myocardial infarction (AMI), initially in cardiogenic shock (CS).

Despite all the advances in the treatment of CS complicating AMI, early reperfusion remains the only therapy that reduces the high risk of death. The most effective restoration of coronary blood flow at the microcirculation level is ensured by mechanical reperfusion (percutaneous coronary intervention) and adjuvant antithrombotic treatment. Inhibitors of ADP-induced platelet activation, i.e., $P2Y_{12}$ inhibitors, are essential to combined antiplatelet therapy. Oral $P2Y_{12}$ inhibitors (e.g., ticagrelor) require hours to take full efficacy, and their effectivity is furthermore impacted by splanchnic hypoperfusion in shock patients. Cangrelor, the only available parenteral $P2Y_{12}$ inhibitor with the immediate onset of action, is an ideal drug to bridge the time gap.

The hypothesis of the study is that intravenous cangrelor will be (a) more effective in terms of the rate of onset and the proportion of patients achieving effective periprocedural inhibition of ADP-induced platelet aggregation, and (b) at least as effective (the calculation of sample size for both superiority and non-inferiority) in reducing major cardiovascular events compared to the recently recommended treatment with crushed oral ticagrelor.

The timeline of the project is given in Figure 1.

Figure 1 Timeline of the project



Inclusion criteria

1. Men and women over 18 years of age.
2. Acute myocardial infarction, as defined by the universal definition of the ESC, ACC, and AHA indicated for emergent percutaneous coronary intervention (primary PCI strategy).
3. Cardiogenic shock at admission resulting from acute myocardial infarction and the presence of ≥ 2 criteria below:
    - Systolic blood pressure (sBP) < 90 mmHg,
    - The need for treatment with vasopressors and/or inotropes,
    - Presence of signs indicating organ hypoperfusion – cyanosis, cold peripheral parts, impaired consciousness, congestive heart failure.
4. Signed informed consent.
5. Women of childbearing potential should be protected from pregnancy throughout the study (relevant for long-term use of ticagrelor). Suitable methods of contraception, in this case, include hormonal contraceptives, barrier methods, or complete withdrawal – as long as it is consistent with the patient's lifestyle.

Exclusion criteria

1. Contraindications to antiplatelet therapy with ticagrelor/cangrelor:
    - Recent (< 6 months) major bleeding,
    - Recent (< 1 month) major surgery/injury,
    - History of intracranial hemorrhage,
    - History of Stroke/TIA,
    - Known ticagrelor/cangrelor intolerance,
    - Severe hepatic impairment,
    - Co-administration of potent CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir).

2. Administration of a loading dose of oral $P2Y_{12}$ inhibitor before admission (clopidogrel ≥ 300 mg, ticagrelor 180 mg, prasugrel 60 mg).
3. Need for concomitant chronic anticoagulant treatment due to atrial fibrillation, artificial valve, thromboembolic disease, etc.

Study endpoints

Primary endpoint – laboratory

- Comparison of the effect of parenteral cangrelor with the recommended crushed ticagrelor treatment on periprocedural ADP-activated platelet aggregation; the periprocedural rate of onset and the proportion of patients who achieve effective* $P2Y_{12}$ platelet receptor inhibition defined by a Platelet Reactivity Index (PRI) value at the end of percutaneous coronary intervention.

  **Platelet Reactivity Index (PRI) less than 50% as measured by the vasodilator-stimulated phosphoprotein (VASP) phosphorylation flow cytometric assay*

Primary endpoint – clinical

- Comparison of the effect of parenteral cangrelor with the recommended crushed ticagrelor treatment on the incidence of major cardiovascular events 30 days after enrollment in the study. The primary clinical endpoint is a composite of all-cause death, myocardial infarction, or stroke* within 30 days, expressed as a proportion of patients with any of these events. The primary clinical endpoint is non-inferiority, and if this is met, then superiority will be tested.

  **Ischemic stroke (intracranial hemorrhage assessed as a BARC 3c bleeding)*

Secondary endpoints

Key secondary efficacy endpoint

- Death, myocardial infarction, urgent revascularization of the infarct-related artery, stent thrombosis, or ischemic stroke within 30 days and one year after study enrollment expressed as a proportion of patients with any of these events.

Key secondary safety endpoint

- Occurrence of bleeding, as defined by BARC type ≥ 3B, within 30 days and one year after study enrollment expressed as a proportion of patients with any of these events.

Other secondary endpoints

The following endpoints will be expressed as the proportion of patients with events:

- Death, myocardial infarction, urgent revascularization of the infarct-related artery, stroke, or major bleeding as defined by the BARC (Bleeding Academic Research Consortium) criteria* on day 30 and one year after study enrollment expressed as a proportion of patients with any of these events.
  **BARC type ≥3B*
- Cardiovascular death, myocardial infarction, urgent revascularization, and heart failure on day 30 and one year after study enrollment.
- Individual components of the primary clinical endpoint on day 30 and one year after study enrollment.
- Heart failure* on day 30 and one year after study enrollment.
  **New heart failure or hospitalization for heart failure*
- Cardiovascular death on day 30 and one year after study enrolment.
- Occurrence of bleeding as defined by BARC type ≥ 3B within 30 days after study enrolment.
- Occurrence of stent thrombosis within 30 days after study enrolment.
- Delayed* aortocoronary bypass surgery due to a risk of bleeding within 30 days after study enrolment.
  **Assessed by the heart team, indicating aortocoronary bypass surgery.*
- Effective* $P2Y_{12}$ platelet receptor inhibition defined by Platelet Reactivity Index (PRI) value 1 hour after PCI.
  **Platelet Reactivity Index (PRI) less than 50% as measured by the vasodilator-stimulated phosphoprotein (VASP) phosphorylation flow cytometric assay*

The following endpoints will be displayed as the median and interquartile range (IQR):

- Duration of vasoactive pharmacotherapy and/or mechanical circulatory support in days.
- Duration of hospitalization* in days.
  **Intensive care unit stay and total hospital stay*
- Maximum values of high-sensitive cardiac troponin in µg per liter.

Other pursued goals

- Cost-effectiveness is expressed as a comparison of the costs of treatment (including days of hospitalization, ICU stays, medical procedures, and pharmacotherapy) and its effect on the occurrence of endpoints. This is measured as the cost per avoided event up to day 30 and up to 1 year after randomization.

Sample size calculation

The original sample size calculation is part of the first version of the protocol, dated June 17, 2018. Based on the available evidence, the power analysis for the primary laboratory endpoint (periprocedural effective platelet $P2Y_{12}$ receptor inhibition, PRI by VASP < 50%) was defined by an endpoint occurrence of 80% in the control group, and an expected endpoint difference of 20%, leading to a sample size of 54 patients. The power analysis for the primary clinical endpoint (death from any cause, myocardial infarction, or stroke within 30 days) in a non-inferiority scenario was defined by an endpoint occurrence of 50% in the control group and an endpoint difference of 10%, with a non-inferiority margin of 5%. This resulted in a required sample size of 270 patients. For the superiority scenario, it was defined by an endpoint occurrence of 50% in the control group and an endpoint difference of 15%, resulting in a sample size of 304 patients.

The recalculation of the study sample size was justified by the significant additional evidence to consider when calculating the size of the study population since the start of the study. A substantial change in ESC guidelines (on myocardial revascularization) for the treatment of patients with AMI complicated by CS was justified by the results of the Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT SHOCK) study. The benefit of culprit-only PCI in reducing the primary endpoint (consisting of death or severe renal failure leading to renal replacement therapy after 1 month, e.g., 45.9% vs. 55.4%) in this study was recognized as clinically important for superiority. This benefit was mainly due to an absolute 8.2% difference in 30-day mortality (51.5% vs. 43.3%).

The CULPRIT shock study sample size was calculated at a difference of 12% in the primary endpoint for superiority. The reduction in the incidence of the primary endpoint was recognized by the guidelines task force as eminent and led to a fundamental change in recommended management.

Power analysis – laboratory primary endpoint (Periprocedural effective platelet $P2Y_{12}$ receptor inhibition, PRI by VASP < 50%)

Power analysis was performed to determine the experimental group's superiority to the control group. The analysis was performed in PASS 13 software (Hintze, J. (2014)). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

The analysis was performed with the following settings:

- Test power 0.8
- Statistical significance level 0.05
- Endpoint occurrence in the control group 70%
- Endpoint difference 20%.

Based on the event rates of 70% in the control group and 90% in the cangrelor group, 124 patients are needed to test the null hypothesis of no difference between groups. The required sample size fits the reachable number of VASP measurements, which is approximately 150.

Power analysis for the primary clinical endpoint (death from any cause, myocardial infarction, or stroke within 30 days)

Power analysis was performed for two scenarios: (i) the experimental group's non-inferiority and (ii) the experimental group's superiority to the control group. The sample size is computed for the patients who will receive the initial dose of the study drug. The analysis was performed in PASS 13 software (Hintze, J. (2014)). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Power analysis for non-inferiority scenario

The analysis was performed with the following settings:

- Test power 0.8
- Statistical significance level 0.05
- Endpoint occurrence in the control group based on relevant studies 50%
- Endpoint difference 10 % with a noninferiority margin of 1%.

Based on the event rates of 50% in the control group vs. 40% in the Cangrelor group and the noninferiority margin of 1%, 506 patients are needed to test the noninferiority hypothesis.

Power analysis for the superiority scenario

The analysis was performed with the following settings:

- Test power 0.8
- Statistical significance level 0.05
- Endpoint occurrence in the control group based on relevant studies 50%
- Endpoint difference 12%.

Based on the event rates of 50% in the control group vs. 38% in the Cangrelor group, a total of 536 patients is needed to test the null hypothesis of no difference between groups. Allowing for a 3% drop-out rate, 550 patients should be enrolled. The drop-out rate is based on settings of multiple clinical studies, and a higher drop-out rate is not expected in our study.

Schedule of study visits

The study started in August 2018 and reached N=304 enrolled patients in August 2021, as planned in the original version of the protocol. The end of the collection of the extended sample size, according to AMENDMENT 2 of the study protocol, is planned for January 2024. For each patient, the following order of case report forms is planned (Table 1):

- Randomization,

- Visit 1 - admission to the hospital on the first day,
- Visit 2 – Follow-up on day 7,
- Visit 3 – Follow-up on day 30 ± 5 days,
- Visit 4 – Follow-up at year 1 ± 14 days.

For all clinically planned measures, visits should occur within a time window of the scheduled visit. Visits outside the visit window are regarded as protocol deviations. The target day and visit window are defined in the protocol.

Table 1 Scheduled visits

	Randomization Visit 1	Day 7 Visit 2	Day 30 ± 5 days Visit 3	Year 1 ± 14 days Visit 4
Clinical condition	X	X	X	X
ECG	X	X	X	X
Echocardiography	X	X	X	X
[#]MRI	-	X	X	X
[§¶]Laboratory sampling	[§¶]X	[¶]X	[¶]X	[¶]X
Questionnaire of quality of life (EuroQoL 5D)	-	-	X	X

[#]MRI substudy – in selected centers. Laboratory examination involves the following: [§]examination of the effectiveness of antiplatelet therapy by the determination of VASP phosphorylation via flow cytometry – in selected centers; [¶]hematological and biochemical blood tests. ECG: electrocardiogram; MRI: magnetic resonance imaging; VASP: vasodilator-stimulated phosphoprotein

Timing of final analysis

Final analysis is planned when every patient has reached 1 year of follow-up, all data have been entered, verified, and validated, and the primary database has been locked.

Electronic database for the data collection - eCRF (electronic Case Report Form)

Data from individual visits will be entered into the electronic database. The TrialDB online tool will be used for randomization and data collection, providing robust eCRF generation capabilities, hierarchical user rights management, and a user-friendly web interface. The system provides predefined validation rules, variable recalculations, and variable relationship considerations. User access is controlled by a hierarchical system of user rights and user roles. Operations in the database are stored for auditing and change-tracking purposes. The physical security of servers, authorized access, and backup procedures ensure data security. At the same time, a screening log will be maintained, including patients with acute myocardial infarction who have not been enrolled in the study for any reason, and the reasons for non-inclusion will be recorded. The

screening log will include the patient's phone contacts or relatives' phone contact information to verify their medical condition after discharge.

Healthcare facilities involved in the clinical trial will provide access to the source data, documents for clinical trial monitoring, audits, ethics committee oversight, and regulatory authority inspections.

Data management

Data security within the study database is of key importance. Data of individual project are stored in a database system based on a modified version of the TrialDB web-based system for the data collection, which was developed by the Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Czech Republic, on the base of TrialDB system (Brandt et al. l, 2003). This online system has changed its layout and structure, making data entry even more convenient, while maintaining security measures at the same level. The system is designed as a robust foundation for collecting substantial amounts of data in clinical trials and/or clinical registries. It is fully customized to the structures of individual projects. The online application is accessible to users through a web browser. The security of individual records within the database is guaranteed via de-identified data collection. The identity of each patient is replaced with an identification number (ID), which does not allow any backward identification of that person. The unequivocal identification of a patient is only known to the attending physician or authorized health care professional.

Randomization

The patient will be randomized after the informed consent form has been signed. As this is an acute condition, an abbreviated version of the informed consent form (one-page A4 format) will be available to the patient following applicable law. After the patient's condition has stabilized, a full version of the informed consent form will be presented to the patient (consent to continue in the clinical trial). The full and abbreviated versions of the informed consent form are attached to the final version of the protocol.

An online database system (TrialDB) provides randomization for data collection. After entering basic patient data (age, gender, body weight, type of acute myocardial infarction, and mechanical ventilation upon admission), a study arm inclusion and a randomization code are generated based on a predefined randomization scheme. The patients are randomized in a 1:1 allocation ratio using random permuted blocks, with the size of block four stratified by the center.

Unblinding

The study is double-blind. However, in the case of a clinically emergent situation in which knowledge of the treatment is essential, it is possible to “unblind” the administered medication during the first four hours after randomization (i.e., to obtain information on which of the drugs -

cangrelor or ticagrelor is being used to treat the patient in the first four hours). This situation is recorded using an online eCRF option. In the further course of the study, all patients are treated with ticagrelor.

Randomization of patients with impaired consciousness

Acute myocardial infarction complicated by CS is a life-threatening situation. The manifestation of circulatory failure is often accompanied by simultaneous disturbances of consciousness, the need for artificial lung ventilation, or mechanical circulatory support. If, for these reasons, obtaining informed consent before inclusion in the clinical trial is not possible, the consent of the patient's representative is required. If this representative is not appointed or available, the patient will be enrolled after an independent witness has signed the informed consent form, confirming through their signature that the trial subject has been enrolled according to the procedure outlined in the protocol approved by the ethics committee (date, name, and signature). The patient's consent to continue in the study will be obtained immediately after the patient's health status improves.

Validation of data collection

The TrialDB system serves as a critical component of the data management infrastructure, specifically designed to validate the completeness and accuracy of the mandatory variables captured in the eCRF for each enrolled participant. This system systematically reviews the data entries to ensure compliance with predefined data entry standards, identifying any discrepancies, omissions, or errors in the mandatory fields. Following this validation process, the system generates comprehensive validation reports, including a detailed list of all detected issues, such as missing or incorrect data points, and a list of patients with invalid or incomplete records. These reports are then distributed to each participating study site on a regular monthly basis to allow for timely corrective actions, ensuring that the data remains accurate, consistent, and complete throughout the trial. The automated validation procedure is repeated regularly until the data issue is solved to ensure the completeness of the records. The automated validation procedures are supplemented, if necessary, by extraordinary validations communicated through the data management team.

In addition to this automated data validation process facilitated by the TrialDB system, the study will undergo an additional layer of oversight through independent monitoring conducted by a dedicated clinical research associate. This independent monitoring will involve on-site or remote monitoring visits at regular intervals, depending on the study protocol, with the specific goal of verifying the integrity and authenticity of the data recorded in the eCRF. Throughout the study, the external monitor will systematically compare the data entered into the eCRF against the source documents, including patient medical records, laboratory results, and other relevant clinical documents. This comparison ensures that the eCRF data accurately reflects the true patient outcomes and clinical events while identifying any discrepancies that may require

resolution. The error reports and their resolution are evaluated and stored by the external monitor. In addition to the regularly scheduled validations stated above, the internal audit is conducted by the study management in case of serious data issues and at the end of the data collection.

The dual approach of automated electronic validation through TrialDB and manual verification by a monitor and investigating team aims to uphold the highest data quality standards, ensuring that the data submitted for analysis are accurate and reliable, thereby enhancing the overall integrity of the study findings. The final validation of endpoints is provided by the endpoint adjudication committee and approved by its chairperson. Each endpoint is evaluated by two independent experts, with a third expert resolving any disagreements, ensuring robust and unbiased endpoint classification.

Statistical analysis

Statistical software and responsibilities

The data will be reviewed and statistically processed in the statistical analysis center: Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Jiri Jarkovsky, MS.c. Ph.D. The analysis will be computed using SPSS 27.0.1 (IBM Corporation, 2021).

Handling of missing values and outliers

Missing values are subject to validation procedures and will be communicated with study sites using lists of detected problems. If correction of missing values is not possible, no imputation of missing values will be performed. The presence of outliers will be evaluated using visual inspection of the continuous variable distribution; detected outliers will be removed from the statistical computations.

Interim analysis

No interim analysis is planned for this study; the decision can be justified as follows:

Reduction of Type I Error: Conducting interim analyses introduces the risk of inflating the Type I error rate. By avoiding interim analyses, the SAP maintains the integrity of the statistical significance threshold (e.g., a p-value of 0.05).

Pragmatic Feasibility: Given the acute nature of myocardial infarction with cardiogenic shock, the timeline for endpoint occurrences (30 days for primary endpoints) is relatively short, reducing the value of interim results for decision-making purposes.

Cost and Logistical Considerations: Implementing interim analyses would require additional resources, such as re-randomization schemes, database locks, and independent review committees, which are unjustified given the study's endpoints and anticipated outcomes timeline.

To mitigate risks associated with the absence of interim analysis:

- External monitoring is performed by an independent Clinical Research Associate (CRA), which provides regular site monitoring and data validation to ensure data quality and patient safety.
- The Data Safety Monitoring Board (DSMB) periodically reviews accumulated safety data, including adverse event frequencies and severity, to address any unexpected risks promptly.

Substudies

The following substudies are planned:

- Echocardiographic substudy,
- Magnetic Resonance Imaging substudy.

Subgroup analysis

The analysis of the following subgroups is planned in the study:

- Women versus men,
- Patients with prehospital time delay duration 3 hours and longer versus less than 3 hours,
- Patients with and without out-of-hospital cardiac arrest,
- Patients with and without mechanical ventilation,
- Patients with and without mechanical circulatory support (e.g., IMPELLA, ECMO)*
- Patients with and without persistent coma (Glasgow Coma Scale < 8) at admission,
- Patients with and without diabetes,
- Patients with and without obesity,
- Patients who are cigarette smokers versus non-smokers,
- Patients with and without multivessel disease,
- Patients with and without a history of heart failure.

**A time-dependent covariate analysis will be performed instead of standard subgroup analysis to prevent bias due to treatment-dependent selection effects for mechanical circulatory support (MCS), which may occur post-randomization.*

Handling of Post-Randomization Events (MCS)

MCS use will be modeled as time-dependent covariates in survival analyses to avoid bias introduced by post-randomization treatment effects. These covariates will be introduced into the primary and secondary outcome models as follows:

Time-Dependent Covariate Analysis

To accurately account for the influence of MCS on study outcomes, these variables will be modeled as time-dependent covariates within the Cox proportional hazards model:

Primary Model:

- $HR=\beta1(\text{Treatment})+\beta2(\text{Mechanical Ventilation (time-dependent)})+\beta3(\text{ECMO (time-dependent)})+\epsilon$
- This ensures that the estimation of treatment effects is not confounded by patients who deteriorate and need additional support after randomization.

Competing Risks Model (Fine & Gray) for Non-MACE Outcomes:

- If MCS is strongly associated with mortality before the primary endpoint, a competing risks approach will be applied using the Fine & Gray subdistribution hazard model.

Sensitivity Analysis

- Inverse Probability of Treatment Weighting (IPTW) will be applied as an alternative approach to adjusting for potential differences between patients requiring MCS and those who do not.

Reporting & Interpretation

- The Kaplan-Meier curves for MACE outcomes will be stratified based on whether patients required MCS, but formal statistical comparisons will be limited to time-dependent Cox models to avoid survivor bias.
- Forest plots will be presented for pre-randomization subgroups only.

Analysis population

The patients enrolled in the study will be summarized in a CONSORT flow diagram. The analyses will be conducted using a modified intention-to-treat principle (MITT), an intention-to-treat principle (ITT), and a per-protocol (PP) approach. The MITT population includes all randomized patients in the trial who received a dose of the study drug. The ITT encompasses all trial-randomized patients, and the PP population consists of all randomized patients who received the full dose of the study drug as per protocol. Treatment classification in all scenarios will be based on the randomized treatment. The MITT will serve as the primary analysis approach; analyses based on ITT and PP populations will be considered secondary and confirmatory.

Data Sharing

The data used in the published scientific papers will be available according to the requirements of the respective scientific journals. To mitigate the risk to patient privacy, the data will be

anonymized and identified through masking or generalization of direct and some indirect identifiers. Only variables used in the given analysis will be included in the shared dataset.

Statistical analysis

Standard descriptive statistics will be employed in the analysis to summarize both categorical and continuous variables. For categorical variables, data will be presented as absolute frequencies (i.e., counts) and relative frequencies (i.e., percentages), clearly representing each category's distribution across the study groups. For continuous variables (including pharma-economic data), the data will be reported either as the median supplemented with the interquartile range (IQR) or the 5^{th} to 95^{th} percentiles range, which captures the central tendency and spread in a non-parametric manner or as the mean supplemented with the standard deviation, which provides a measure of central tendency and variability under the assumption of normal distribution. The choice between median and mean reporting will depend on the distributional properties of the continuous variables. Data visualization will use standard box and whisker plots for continuous variables and bar plots for categorical variables. Relative risks and 95% confidence intervals will be used to describe and visualize the results of endpoint analysis.

The chi-square test will be employed for categorical variables, including the primary and secondary study endpoints and all other relevant categorical data, to assess the statistical significance of observed differences between groups. This test will evaluate whether the observed frequencies in different categories deviate from what would be expected under the null hypothesis. The Mann-Whitney U test will be applied for continuous variables, as it is a robust non-parametric alternative to the t-test, particularly useful when the assumption of normality is not met. This test will determine whether there are statistically significant differences in the distribution of continuous variables between the study arms. The non-inferiority scenario will be assessed using a one-sided Z-test with a non-inferiority margin of 1%.

To ensure comparability among centers, the data for analyzing maximum values of high-sensitivity cardiac troponin will be presented as the ratio of the maximum value within seven days to the reference value for myocardial infarction at a specific center.

A p-value of 0.05 will be adopted as the threshold for determining statistical significance across all analyses. All statistical analyses will be conducted in strict accordance with the regulatory guidelines outlined in the E9 Statistical Principles for Clinical Trials document published by the U.S. Food and Drug Administration (FDA) under the reference FDA-1997-D-0508. These guidelines ensure that the statistical methods employed adhere to established clinical trial data analysis standards, ensuring rigor, reproducibility, and validity of findings.

Variables and tables will be presented in the order in which the sections are shown in the eCRF. Parameters recorded in more than one SI unit (e.g., lab units) will be converted into a single SI unit as appropriate.

Description of patients' characteristics

Prior to the analysis of the primary and secondary endpoints, the treatment groups (or any groups in subgroup analyses) will be compared about the following patients' characteristics:

- Demographics: age, sex, body weight, body mass index (BMI), obesity, and cigarette smoking.
- Characteristics of AMI at admission: type of acute myocardial infarction (STE- or NSTE-MI), mechanical ventilation upon admission.
- Time delay: from symptoms to hospital, from symptoms to reperfusion.
- Out-of-hospital cardiac arrest: cardiopulmonary resuscitation before admission, first documented rhythm, time to return of spontaneous circulation (ROSC) (min), external cardiac massage - before admission, on admission, overall duration, mechanical ventilation, regulation of body temperature, target value.
- Patient´s status at the time of admission: blood pressure - left arm systolic/diastolic (mmHg), blood pressure - right arm systolic/diastolic (mmHg), pulse rate (BPM), cyanosis, mydriasis, transient mydriasis, deep unconsciousness without prior treatment with hypnotics.
- Treatment with vasopressors and/or inotropic agents, noradrenaline, adrenaline, dopamine, dobutamine, another vasopressor agent, another inotropic agent.
- Analgosedation: analgosedation, opioid (morphine, fentanyl, sufentanil), benzodiazepine (midazolam, diazepam, other), propofol, another analgosedation method.
- Medical history: hyperlipidemia, hypertension, diabetes mellitus, previous myocardial infarction, previous PCI, previous CABG surgery, previous implantation of a pacemaker, ICD, CRT, chronic heart failure, chronic kidney failure, chronic liver failure, Child-Pugh score, peripheral vascular disease, peripheral artery bypass, history of bleeding, chronic obstructive pulmonary disease.
- Chronic medication: aspirin, clopidogrel, prasugrel, ticagrelor, beta-blocker, ACE inhibitor, ARB, ARNI, statin or another lipid-lowering agent, furosemide, hydrochlorothiazide (indicated as a diuretic agent), spironolactone, digoxin, ivabradine, proton-pump inhibitors.
- Echocardiography during the admission or first day of hospitalization: LVEF (%), complications of MI: ventricular septal defect, ruptured mitral chordae tendineae, and severe mitral regurgitation; hemodynamically significant pericardial effusion, other.
- Coronary angiography: approach, number of affected vessels, left main coronary artery disease (LMCAD), indication after coronary angiography.

- Percutaneous coronary intervention: artery treated during the PCI: left main coronary artery, left anterior descending artery (ramus diagonalis), circumflex artery (ramus marginalis sinister), right coronary artery; PTCA only; stent implantation: number, total length of stented segments (estimate) in mm, BMS, DES, BVS, another stent; TIMI flow grade through the infarct-related artery before PCI, TIMI flow grade through the infarct-related artery after PCI; complications of PCI; evaluation of the procedural result (optimal, suboptimal, failed PCI); Comment on the procedure.
- Laboratory tests during the visit examination: hemoglobin (Hb) (g/L), hematocrit (HCT) (%), erythrocyte count (RBC) ($x10^{12}$/L), leukocyte count (WBC) ($x10^{9}$/L), platelet count (PLT) ($x10^{9}$/L), urea (mmol/L), creatinine (mmol/L), glycemia (mmol/L), AST (ukat/L), ALT (ukat/L), lactate (mmol/L), CRP (mg/L), ratio of value of high-sensitive cardiac troponin and reference value for MI, total bilirubin (μmol/L), Na (mmol/L), K (mmol/L), arterial blood gas (ABG) pH, pO_2 (kPa), pCO_2 (kPa), base excess (BE) (mmol/L).

Additional analyses

The analysis of the primary and secondary endpoints in the complete study population assumes a balanced distribution of potentially confounding factors between the study arms, which is expected to be achieved through randomization. Considering this assumption, no prior planned multivariate adjustment for the confounding variables will be conducted in the initial analysis of the primary endpoints. However, despite this, further exploratory analyses will incorporate both univariate and multivariate models, such as logistic regression and Cox proportional hazards models, to evaluate the potential influence of specific patient characteristics on the occurrence of the endpoints. This approach will provide a more detailed understanding of how individual baseline factors may affect study outcomes. Additionally, time-to-event data will be visualized using the Kaplan-Meier methodology, allowing for an informative representation of the temporal aspects of endpoint occurrences. Time to the event will be computed from the date of randomization and the date of the analyzed event or the date of last contact in the case of censored patients.

For subgroup analyses, where confounding factors may exhibit an unbalanced distribution across the study arms, they will be incorporated into the multivariate logistic regression models. This will allow for appropriate adjustment for these confounders, providing a more accurate estimation of the association between treatment effects and study endpoints in the presence of imbalances. By accounting for such factors, the analysis will enhance the robustness and validity of the conclusions drawn regarding the study outcomes within the specified subgroups.

Safety analysis

This phase IV clinical trial focuses on observing and comparing the use of approved medicinal products as part of standard clinical practice. Information regarding side effects will neither be actively collected nor evaluated.

Hospitalizations and life-threatening conditions, which are prerequisites for study enrollment, are not categorized as serious adverse events (SAEs). The investigator will perform causality assessments, and immediate reporting of adverse events unrelated to the study will not be required.

In routine clinical practice, cardiogenic shock has a mortality rate of over 50%. Deaths unrelated to the study will be summarized and included in annual study reports.

References

Brandt CA, Deshpande AM, Lu C, Ananth G, Sun K, Gadagkar R, Morse R, Rodriguez C, Miller PL, Nadkarni PM. TrialDB: A web-based Clinical Study Data Management System. AMIA Annual Symposium Proceedings 2003, 2003: 794. PMID: 14728299, PMCID: PMC1480035.

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