Danish-German cardiogenic shock trial—DanGer shock: Trial design update

Jacob Eifer Møller, MD, PhD, DMSc,⁎, and Oke Gerke, PhD, †,‡, on behalf of DanGer Shock Investigators*  
Odense, Denmark; Copenhagen, Denmark

Abstract

Background The main objective of the Danish German Cardiogenic Shock trial (DanGer Shock ClinicalTrials.gov Identifier: NCT01633502) is to assess the efficacy of the trans valvular axial flow device Impella CP in treating patients with AMICS shock due to STEMI undergoing emergency percutaneous coronary intervention.

Methods This statistical analysis plan represents an overview of the statistical methods which will be used for analyzing the DanGer Shock trial.

Results The primary study endpoint is death from all causes through 180 days in the intention to treat population (all randomized consented patients). The secondary endpoints comprise; composite event of the need for additional mechanical support, need for cardiac transplantation, and death of all causes whichever comes first; and days alive and out of hospital. As exploratory analyses an as treated analysis of primary endpoint will be performed. Composite safety endpoint will comprise of major bleeding, vascular complications, device malfunction, damage to the aortic valve, and significant hemolysis. The primary endpoint death rate at 180 days will be analyzed using Cox proportional hazards analysis. The result will be reported as hazard ratio and corresponding 95% confidence interval (95% CI). No imputation of missing values will be performed. Additional statistical analyses for predefined hemodynamic, metabolic, renal, hematological, and health economics substudies will be specified in separate protocols.

Conclusion Main analyses of the primary and secondary outcomes of the DanGer Shock trial will be conducted according to this publication. (Am Heart J 2023;255:90–93.)

Cardiogenic shock complicates acute myocardial infarction in 5% to 10% of AMI cases. Despite immediate revascularization, pharmacological and in selected cases mechanical circulatory support mortality often exceed 50%. In ST segment elevation AMI (STEMI) cardiogenic shock is typically a consequence abrupt decrease in cardiac output causing tissue hypoperfusion and organ failure. Active ventricular unloading with transvalvular axial flow devices seems promising for restoration of cardiac output without increasing myocardial oxygen consumption. Evidence to guide this treatment is low and the use is based on expert consensus, conflicting retrospective studies, and small underpowered randomized trials. Thus, equipoise exists on the benefit of mechanical circulatory support in AMI cardiogenic shock (AMICS).

The main objective of the DanGer Shock trial is to assess the efficacy of the trans valvular axial flow device Impella CP (Abiomed, Danvers, MA) in treating patients with AMICS due to STEMI undergoing emergency percutaneous coronary intervention (PCI).

Endpoints

Primary endpoint

The primary study endpoint is death from all causes through 180 days in the intention to treat population (all randomized consented patients).

Secondary endpoints for main analysis comprise

1. Composite event of the need for additional mechanical support (short and/or long-term), need
for cardiac transplantation, and death of all causes whichever comes first.
2. Days alive and out of hospital: calculated by subtracting the number of days spent in hospital, from time of randomization to end of follow-up (180 days) for each patient.

Exploratory analyses
Exploratory analyses comprise an as treated analysis of primary endpoint. As treated population is defined as patients fulfilling the in- and no exclusion criteria (Supplementary data) excluding patients with crossover, which is considered in patients that are randomized patients to control where Impella CP was placed as mechanical circulatory support, and patients in intervention group where no attempt to place Impella CP was commenced. Further, an analysis of composite cardiovascular events including rehospitalization for acute coronary syndrome and heart failure or death from all causes (hospital survivor analysis only) until 180 days will be performed.

Adverse events
Composite safety endpoint will comprise of major bleeding, vascular complications, device malfunction, damage to the aortic valve, and significant hemolysis. The individual components of the composite safety endpoint and use of renal replacement therapy, septic shock, ventricular fibrillation or ventricular tachycardia requiring cardioversion during cath lab and ICU treatment, stroke, and pneumonia during mechanical ventilation will be reported individually.

Hypothesis and sample size estimation
The primary endpoint is the occurrence of death from all causes. In patients with STEMI and cardiogenic shock, the null ($H_0$) hypothesis is that the intervention group managed with the Impella CP device placed when shock is diagnosed will have a death rate at 180 days that is equal to the observed death rate for control group. The alternative hypothesis ($H_a$) is that the Impella CP group will have a different death rate from the control group. Rejection of the null hypothesis with a lower death rate for the Impella CP group will signify that the Impella CP is superior to the control on the primary endpoint. The parameters/assumptions for the above hypothesis are:

- The death rate in the control group at 180 days is 60%.
- Expected treatment effect is absolute 18%, resulting in a death rate in the Impella CP group equal to 42%.
- The power of the study is 80%.
- The 2-sided alpha is 5%.

A minimum of 162 subjects per arm equaling 165 primary events will provide 80% power to reject the null hypothesis in favor of the alternative hypothesis. To account for dropout, 360 patients will be randomized or if observed mortality is lower than expected enrollment will continue until 165 events have been recorded.

General statistical considerations
In brief, continuous data will be analyzed using parametric statistical methods. Only if parametric assumptions cannot be satisfied, comparable nonparametric procedures will be used. Parametric model assumptions will be assessed using Normal-plot or Shapiro-Wilks statistic for verification of normality and Levene’s test for verification of homogeneity of variances. Categorical variables will be presented as number and percent. Baseline characteristics, hemodynamic and metabolic status at randomization, and procedural data will be presented in tabular form for the intention-to-treat population. The comparability among treatment groups will be evaluated with respect to all clinically relevant demographic and baseline characteristic variables; continuous variables will be analyzed by 2-sample $t$ tests (nonparametric alternative: Wilcoxon’s rank sum test), and categorical variables will be tested using Pearson’s $\chi^2$ test for contingency tables (alternatively with Fisher exact test). All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha = 0.05$ (2-sided), except for those specified otherwise.

Interim analysis
One interim analysis will be performed after 180 patients have been followed until death or 180 days, using the O’Brien-Fleming significance level approach. A rejection of the primary null hypothesis with a $P$ value that falls below 0.05527 (STATA, procedure landemets, $N = 324, n = 180, t = 0.5556$) will trigger the possibility for early stopping to be discussed by the Data Safety Monitoring Board (DSMB). The analysis will be performed blinded for treatment allocation by an independent statistician, which is a member of the DSMB. At the interim analysis the overall mortality rate will be assessed, and it will be evaluated whether the event rate is adequate to meet the assumption of the sample size calculation. DSMB will recommend continuation or termination of the trial based on this.

Analysis of primary endpoint
The primary endpoint death rate at 180 days will be analyzed using Cox proportional hazards analysis after testing that the assumption of proportional hazards is met. The primary analysis will be an unadjusted analysis of treatment effect. Secondary a multiple Cox proportional hazards analysis will be performed with adjustment for randomization strata, culprit lesion (LM/LAD vs other) and country (Denmark and Germany/United
Analyses will be performed in the intention-to-treat population. The result will be reported as hazard ratio and corresponding 95% confidence interval (95% CI) and will be presented in a Kaplan-Meier plot. The analysis of the primary endpoint will be performed with a 2-sided \( \alpha = 0.048 \) to adjust for one formal interim analysis.

Predefined subgroup analyses will be performed for biological sex, median age, median lactate at randomization, median MAP at randomization, median LVEF at randomization, anterior myocardial infarction vs infarct at another location, single vs 2/3-vessel disease, time of randomization (2013-2018 or 2019-2023), and SCAI class at randomization (C vs D/E). A Forest plot of the relative risk for the primary endpoint and 95% confidence intervals resulting from univariate comparisons between the treatment groups will be shown for these subgroups.

The DanGer Shock trial will be considered successful only if Impella CP is shown to be significantly superior to control on the primary endpoint. However, in the event Impella is not shown to be significantly superior to control on the primary endpoint, analyses on the secondary endpoints and substudies will still be carried out in order to assess other variables which might be candidates for future studies but will be hypothesis generating.

Analyses of secondary endpoints

The secondary composite endpoint of major cardiac events will be analyzed using Cox proportional hazards analysis after testing that the assumption of proportional hazards is met. This will be done as unadjusted analyses of treatment effect and presented as hazard ratio and corresponding confidence intervals adjusted for multiple outcomes according to the procedure specified by Jakobsen et al. With 2 secondary outcomes, the adjusted \( P \) values for the secondary outcomes will be below .0575, equivalent to an adjusted CI of 96.25%. Data will be presented in Kaplan-Meier plot when appropriate.

Analyses of adverse events

Descriptive statistics will be used to summarize and analyze the safety parameters. Adverse events will be summarized for each treatment group by tabulating the number of incidents and number of patients for each individual adverse event and the composite adverse event. Results will be reported as relative risk with 95% confidence intervals.

Missing data

All centers will be encouraged to obtain as complete data as possible and optimized with 100% monitoring of data by an independent Contract Research Organization. Missing values for the primary endpoint will be minimal to none in Denmark where survival status will be cross-checked with Danish regulatory registries where all deaths in the country are recorded and linked to a unique personal identifier. All attempts will be made to ensure vital status of patients randomized in Germany but the risk of loss to follow-up within 180 days exists. In the event of loss to follow-up patients will be censored at the last date at which respective patient data was recorded. For all other variables, no imputation of missing values will be performed.

Substudies

Additional statistical analyses for predefined hemodynamic, metabolic, renal, hematological, and health economics substudies will be specified in separate protocols.

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Conflict of interest

The DanGer Shock trial is funded by Abiomed and JEM has reviewed speakers fee from Abiomed.

References

