Deferring arterial catheterization in critically ill patients with shock – EVERDAC trial

STATISTICAL ANALYSIS PLAN — December 2024

The initial Statistical Analysis Plan established before launching the study and published in BMJ Open in 2021 **(**Muller G et al. BMJ Open 2021;11:e044719. doi:10.1136/bmjopen-2020-044719) was amended after the blind review of the data in December 2024.

Level of statistical significance

Statistical significance threshold will be set at 5%, and 95% two-sided confidence intervals (95%CI) will be calculated for all estimates.

Analyzed population

All randomized patients, except for patients who secondarily object to the use of their data or protected under guardianship, will be included in the analysis. No interim analysis will be performed. Two per-protocol populations were defined during the blind review:

- In the first per-protocol population, we will exclude patients wrongly included, and patients from the noninvasive group in whom the arterial catheter previously inserted was not removed after the randomization. In the invasive group, we will exclude the patients who either did not undergo an attempt at arterial catheter insertion or had the arterial catheter insertion more than 24h after randomization.
- In the second per-protocol population, we will exclude patients from the invasive group who did not receive an arterial catheter within 24h after randomization, regardless of the reason (unsuccessful arterial catheter insertion, no attempt of arterial catheter insertion or insertion occurring more than 24h after randomization). The per-protocol population in the noninvasive group will remain unchanged for the second per-protocol analysis.

Description of baseline characteristics

All data recorded at baseline will be summarized by treatment group using means and standard deviation for normally distributed quantitative variables, median and interquartile range for other quantitative variables, and counts and percentages for qualitative variables. No statistical test will be used.

Primary outcome

The primary analysis of the primary outcome will be the determination of the between-group difference (noninvasive group minus invasive group) in rates of day-28 mortality, estimated with a binomial generalized estimating equation (GEE) model with identity link adjusted on the stratification variables and on the center effect (Pedroza 10.1186/s12874-016-0217-0). A switch from noninferiority to superiority is *a priori* planned if the hypothesis of noninferiority with a noninferiority margin of 5 percentage points is verified. These hypotheses will be assessed using the stratified Farrington-Manning test for differences in proportions.

Secondary outcomes analysis

Statistical analyses for secondary outcomes will not be adjusted for multiplicity; therefore, secondary-outcome findings should be interpreted as exploratory.

- Day-90 mortality will be analyzed with the same model as the primary outcome .
- Cumulative incidence of death from randomization through Day 90 will be analyzed with a Cox model.
- ICU mortality and hospital mortality will be analyzed in a competing risks framework. A hazard ratio will be computed from the whole groups using a Fine and Gray regression model. ICU discharge or hospital discharge will be considered as competing events.

The following outcomes will be described with median and quartiles and compared between groups using median differences:

- Duration of ICU stay from randomization to discharge.
- Duration of hospital stay from randomization to discharge.
- Duration of mechanical ventilation from randomization and Day 28.
- Ventilator-free days from randomization to Day 28.
- Renal replacement therapy-free days from randomization to Day 28.
- Vasopressor therapy-free days from randomization to Day 28.

For each outcome, 95% confidence intervals of the median difference will be computed using unstratified bootstrapping (10,000 samples with replacement). Vasopressor therapy-free days, renal replacement therapy-free days and duration of mechanical ventilation do not account for the competing risk of death.

The following outcomes will be represented with boxplots at each day:

- Evolution of daily SOFA score during the first seven days after randomization. This outcome will be analyzed with a linear mixed model with time (considered as a quantitative variable) and the intervention group as fixed effects, an interaction term between group and time, and a random effect on the patient, The regression terms will be estimated with their 95% confidence intervals, with the noninvasive group as the reference. The same model will also be analyzed with time considered as a qualitative variable in the aim to describe the mean difference between groups at each time, using contrasts.
- Mean daily blood volume drawn for laboratory testing during ICU stay.
- Evolution of blood hemoglobin level from randomization to Day 28.
- Evolution of hematocrit from randomization to Day 28.
- Daily amount of intravenous fluid given for rapid vascular volume expansion during the first seven days after randomization.
- Daily fluid balance during the first seven days after randomization.

The following outcomes will be analyzed with a difference of proportions:

- Proportion of patients treated by renal-replacement therapy between randomization and Day 28.
- Proportion of patients treated by vasopressor between randomization and Day 28.

The time free of arterial catheter insertion, from randomization through Day 90 will be graphically represented with cumulative incidence curves.

The following outcomes will be analyzed with the use of a quasi-Poisson regression model and expressed as rate ratios, with the duration of stay in the ICU as the offset:

- Number of arterial and central venous catheter insertion during ICU stay from randomization to Day 28.
- Number of blood cultures performed during ICU stay from randomization to Day 28.
- Number of blood draws from the venous catheter during ICU stay from randomization to Day 28.
- Number of attempts at arterial puncture during ICU stay from randomization to Day 28.
- Number of red blood cell packs transfused during ICU stay from randomization to Day 28.
- Numbers of arterial and central venous catheter-related bloodstream infections during ICU stay from randomization to Day 28.

Safety outcomes and analyses

- The number of adverse events of special interest will be described in each group and compared using a chi-squared test.

Patient-reported pain and discomfort related to the device used for BP monitoring will be measured daily using 4 scales rating from 0 to 10. Each day, a patient will be considered as experiencing pain and/or discomfort if at least one scale is ≥ 4 (Gerbershagen, DOI: 10.1093/bja/aer195). The proportions of patients experiencing at least one day with pain and/or discomfort will be compared with a chi-squared test. The numbers of days with pain and/or discomfort will be compared between the groups with the use of a quasi-Poisson regression model and expressed as rate ratios, with the duration of stay in the ICU as the offset.

- The number of patients reaching the predefined upper limit of vasopressor dosage (>2.5µg/kg/min of norepinephrine tartrate plus epinephrine) will be estimated in each group, and day 28 mortality will be described amongst these severely ill patients.

Subgroup analyses

No subgroup analyses were prespecified.

Implementation

Statistician: Dr Elsa Tavernier , Centre d'Investigation Clinique INSERM 1415, CHRU de Tours.
Software: R version 4.3.1

SUMMARY OF CHANGES FROM THE INITIAL PROTOCOL AND JUSTIFICATIONS

Changes in the analyses of the primary outcome

Additional methodological recommendations were identified on current recommendations to estimate a difference in proportions (Pedroza 10.1186/s12874-016-0217-0), recommendations on adjusting stratification variables (Sullivan 10.1002/sim.10060) and recommendations on taking account of the center effect for multicenter studies (Kahan 2013 10.1002/sim.5667, Pedroza 10.1186/s12874-016-0217-0). The final GEE model was established during the analysis of the data, as we observed a significant within-center correlation (Intra-class correlation coefficient = 0.02 for day 28 mortality in each group).

To quantify how strongly our data reject the possibility that the true difference exceeds the 5% noninferiority margin, we employed a stratified Farrington–Manning test. This approach formally tests the noninferiority hypothesis and complements the estimation of the between-group difference obtained with the GEE model. This decision was made during the analysis of the data.

Changes in the analyses of the secondary outcomes

Patient-reported pain and discomfort related to the device used for BP monitoring was initially planned to be analyzed as a quantitative outcome but was binarized because of the over-representation of 0 in responses (>78.4%) for each scale and each visit (0 being equivalent to no pain). This analysis was chosen during the analysis of the data.

Contrary to what was written in the initial statistical analysis plan, the analysis of vasopressor therapy-free days, renal replacement therapy-free days and duration of mechanical mechanical ventilation do not account for competing risk of death or ICU discharge. This change was made before the blind review.

Additional safety analysis

Upon reviewing the data, we observed that the number of patients in the noninvasive group who underwent arterial catheterization after reaching the vasopressor dose of 2.5 µg/kg/min—a predefined safety criterion for catheterization—was higher than anticipated. This led us to question whether the high vasopressor dose might have resulted from the intervention, specifically due to potential inaccuracies in blood pressure measurements with oscillometric brachial cuff devices. Consequently, we planned to also report the number of patients in the control group (invasive group) who reached this vasopressor threshold and document the difference between groups.

Missing analyses and secondary outcomes

The following secondary outcomes were initially planned in the original protocol but cannot be analyzed due to lack of access to reliable data.

- Numbers of local infections of arterial and central venous during ICU stay (number of new cases per 1000 catheter-days).
- Numbers of arterial and central venous catheter-related infections during ICU stay, expressed as the incidence of new cases per 1000 ICU-days, including local and catheter-related bloodstream infections as consensually defined.
- Number of bloodstream infections during ICU stay, catheter-related or not.
- Number of peripheral venous punctures for laboratory tests.

The protocol published in BMJ open stated that a sensitivity analysis would be adjusted on the location of the arterial catheter. This analysis was removed before the blind review.

Further clarifications

For median differences, confidence intervals are computed using unstratified bootstrapping (10,000 samples with replacement). This precision was added before the blind review.