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Statistical Analysis Plan for the Early Goal Directed Therapy Using a Physiological Holistic View – The ANDROMEDA-SHOCK: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND

ANDROMEDA-SHOCK is an international, multicenter, randomized controlled trial comparing peripheral perfusion-targeted resuscitation (PPTR) versus lactate-targeted resuscitation (LTR) in patients with septic shock, to test the hypothesis that resuscitation aimed at peripheral perfusion will be associated with lower morbidity and mortality.

OBJECTIVE

To report the statistical analysis plan for the ANDROMEDA-SHOCK trial.

METHODS

We describe the trial design, primary and secondary objectives, patients, methods of randomization, interventions, outcomes, and sample size. We describe our planned statistical analysis for primary, secondary and tertiary outcomes. We also describe subgroup and sensitivity analyses. Finally, we provide details for presenting our results including mock tables for baseline characteristics, evolution of hemodynamic and perfusion variables, and treatment-effect on outcomes.

CONCLUSION

According to the best trial practice, we report our statistical analysis plan and data management plan prior to locking the database and starting analyses. We anticipate that this document will prevent analysis bias and enhance the utility of the reported results.

Trial registration: ClinicalTrials.gov, number NCT03078712

INTRODUCTION

BACKGROUND AND RATIONALE

Early recognition of tissue hypoperfusion and its reversion in septic shock are key factors to improve survival.[1] Hyperlactatemia has been traditionally considered as a hallmark of ongoing tissue hypoxia[2] and therefore, normalization of lactate levels has been recommended as a resuscitation target.[3] However, other non-hypoperfusion related causes of hyperlactatemia might predominate in an unknown number of patients leading to the risk of over-resuscitation.[4]

Peripheral perfusion could be used as a potential alternative resuscitation goal.[5-8] The excellent prognosis associated with capillary refill time (CRT) recovery, its rapid-response time to fluid loading, its relative simplicity, its availability in resource-limited settings, and its capacity to change in parallel with perfusion of physiologically relevant territories constitute strong reasons to evaluate the usefulness of CRT to guide resuscitation in septic shock patients.

ANDROMEDA-SHOCK is an international, multicenter, randomized controlled trial comparing peripheral perfusion-targeted resuscitation (PPTR) versus lactate-targeted resuscitation (LTR) in patients with septic shock, to test the hypothesis that resuscitation aimed at peripheral perfusion will be associated with lower morbidity and mortality.

This article outlines the statistical analysis plan (SAP) for ANDROMEDA-SHOCK with the aim of preventing statistical analysis bias arising from exploratory analyses after the study results are known. The SAP was developed following appropriate guidelines[9] prior to locking the trial database and starting analyses.

OBJECTIVES

Primary Objective

Our primary objective is to determine if PPTR is associated with lower mortality rates within 28-day than a LTR in patients with septic shock.

Secondary objectives

Our secondary objectives are to determine if, in patients with septic shock, a PPTR compared to LTR can decrease all-cause mortality within 90 days; increase mechanical ventilation-free days, renal replacement therapy-free days, and vasopressor-free days within 28 days; decrease organ dysfunction at 72 hours; and decrease ICU and hospital lengths of stay.

METHODS

TRIAL DESIGN

ANDROMEDA-SHOCK is a prospective, multicenter, parallel-group, randomized trial aimed to compare an 8-hours protocol of PPTR *vs.* LTR in patients with septic shock.[10] The trial is being conducted in 26 intensive care units (ICU) in Argentina, Chile, Ecuador, Colombia and Uruguay. The trial protocol (version 1.0 from December, 2016) was submitted and is under review in another Journal, is registered with ClinicalTrials.gov (NCT03078712), and was approved by the Ethics Committee of all the participant institutions. The main study interventions are summarized on Fig 1.

RANDOMIZATION

Eligible patients will be randomly allocated to PPTR or LTR groups. PPTR will be aimed to normalize CRT while LTR will target lactate normalization or a decreasing rate higher

than 20% per 2 hours of lactate levels during the 8-hours of the study period. A randomization sequence with an allocation of 1:1 will be generated by a computer program. Study-group assignment will be performed by means of randomized permuted blocks of eight (without stratification). Allocation concealment will be maintained by means of central randomization. Investigators at the sites will call a representative of the Study Coordinating Center (SCC) available 24-hour / 7-days through a dedicated phone number. The group to which the patient is allocated will only be disclosed after the information is recorded by the SCC. Such a measure prevents the investigator and the medical team from predicting to which treatment group the patient will be allocated.

STUDY INTERVENTIONS

A sequential approach to resuscitation will be followed in both groups as shown in Fig 1. The intervention period will be extended for 8 hours after randomization. All other treatments, during the intervention period and after, will be at the discretion of the treating clinicians according to their local usual clinical practices.

In the PPTR group, capillary refill time will be measured every 30 minutes until normalization and when normalized every 1 h until the end of the 8h protocol. It is measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure will be increased until the skin is blank and then maintained for 10 seconds. The time for return of the normal skin color will be registered with a chronometer. A capillary refill time > 3 seconds will be considered as abnormal.[11]

In the LRT group, lactate will be assessed every two hours during the 8-hour study period.

Fluid responsiveness will be assessed using a structured approach outlined in the protocol, which includes several different predictors (passive leg-raising, end-expiratory occlusion test, pulse pressure variation, respiratory variations of inferior vena cava, aortic velocity time integral) customized according to patients' specific conditions (for example, whether patient is under mechanical ventilation, has irregular cardiac rhythm, ARDS/low respiratory-system compliance).

In patients predicted to be fluid-responsive, the first resuscitation step will be to administer a fluid bolus (500 ml of crystalloids) every 30 min until normalizing capillary refill time in the PPTR group. In the LTR group, fluid boluses will be stopped if at 2h lactate is normalized or has decreased >20%, or previously if after any of the fluid boluses, central venous pressure has increased ≥ 5 mmHg or the patients has become fluid unresponsive.

An open-label vasopressor test will be performed increasing mean arterial pressure up to 80-85 mmHg by using progressive incremental doses of norepinephrine in patients with previous history of chronic hypertension (as defined by previous use of anti-hypertensive medications and medical history) and persistently abnormal capillary refill time or unfulfilled lactate goals accompanied by a fluid unresponsive state. Parameters will be reassessed one hour after in the PPTR and two hours after in the LTR. If after the vasopressor test, capillary refill time improves, and lactate goals are achieved in PPTR and LTR respectively, norepinephrine will be titrated to maintain this new mean arterial pressures goal throughout the study period. If goals are not achieved despite increasing mean arterial pressure, or norepinephrine dose is higher than 0.8 mcg/kg/min or adverse effects are observed (heart rate > 140 ppm, arrhythmias, or evident cardiac ischemia), norepinephrine dose will be reduced to the level before the vasopressor test, and the protocol will move to the next step.

An open-label test of dobutamine at fixed 5 mcg/kg/min or milrinone at fixed 0.25 mcg/kg/min doses (at discretion of the attending physician) will be started in non-hypertensive patients with persistent abnormal capillary refill time or non-achieved lactate goals, and negative fluid-responsive status. Similarly, this open-label test of inodilators will be performed in hypertensive patients with persistently abnormal resuscitation parameters and a failed vasopressor test. Capillary refill time and lactate goals will be rechecked such as in the vasopressor test. If such resuscitation goals are not reached, drugs will be discontinued and no further action will be taken during the study period, except for rechecking fluid responsiveness every hour and restart fluid challenges if the patient gets again fluid responsive. Dobutamine or milrinone doses will be maintained throughout the study period in those favorably responding to the open-label inodilators test, i.e., those showing an improvement in capillary refill time or lactate goals (according to the group assigned). As a safety measure, inodilators will be stopped if heart rate increases >15%, or arrhythmias, ischemia or hypotension develop.

The protocol can be stopped at any moment for safety considerations during the 8h-study period if the attending intensivist considers that the patient has developed unexpected and severe complications or evolves into refractory shock, conditions that under his judgment requires liberalization of management.

SAMPLE SIZE

Mortality in patients with increased lactate levels in circulatory dysfunction has been shown to exceed 40%.[11] In addition, several studies have shown that abnormal peripheral perfusion is associated with a mortality exceeding 40% as well, whereas a normal CRT in

the early phase of septic shock has been associated with a less then 10% mortality.[12,13] We anticipate a mortality within 28-days of 45% in the LTR group of our trial.

A total sample size of 420 patients (210 per group) is expected to provide approximately 90% power to detect a reduction in 28-day mortality from 45% to 30%, analyzing the data using the ITT principle, with a two-sided alpha level of 5%. We consider that a 15% reduction (33% relative risk reduction) in mortality has important clinical value and was observed in earlier resuscitation studies.[13] In addition, this effect size is plausible because limiting fluid administration has been shown to decrease organ failure, the main determinant of death in septic patients.[8]

Nevertheless, we used an adaptive approach,[14] that would allow for a sample-size re-estimation at a preplanned interim analysis after 75% of the sample has been recruited. The sample-size re-estimation was supposed to be conducted by the independent Data and Safety Monitoring Committee (DSMC) only if the size effect observed in the interim analysis is between 10% and 15% absolute reduction in mortality (promising zone) favoring the PPTR over LTR group.[14] The favorable zone was defined as an absolute difference >15% (conditional power >90%) and unfavorable zone as an absolute difference <10% (conditional power <61%) in the interim analysis.

We calculate operational characteristics of this this strategy conducting simulations with 200 studies. Without adaptation, conditional power for the promising zone is between 61% and 90%. In case the study interim analysis felt in the promising zone, adapting sample size up to 840 patients would increase conditional power. Considering a true effect size of 15%, probability of "landing" on promising zone is 22% and mean conditional power would

increase to >90%. Considering a true effect size of 10%, probability of "falling" on the promising zone is 40% and mean conditional power would increase to >80%.

This interim analysis was performed in February 2nd, 2018, and the DSMC recommended to continue the trial with no modifications.

FRAMEWORK

The design of the study is aimed at demonstrating superiority of PPTR over LTR in terms of 28-day mortality and other secondary and tertiary outcomes.

STATISTICAL INTERIM ANALYSES

Interim analyses were conducted after the inclusion of the first 100 patients and at 75% of the sample size (300 patients). Only the independent data and safety monitoring committee (DSMC) had access to results of those analyses. The DSMC is comprised by 5 experienced intensivists and trialists, and 1 senior statistician. The DSMC established no *a priori* statistical stopping guidance according to efficacy, safety or futility. The DSMC recommended that the trial should continue without alterations after those analyses.

TIMING OF FINAL ANALYSIS

All outcomes will be analyzed simultaneously after we have completed the 90-day follow-up of all patients and the database has been locked.

TIMING OF OUTCOME ASSESSMENTS

We will assess outcomes at 8, 24, 48, and 72 hours; at hospital discharge; and at 28 and 90 days,

STATISTICAL PRINCIPLES

Confidence intervals and P values

We will present 95% confidence intervals for effect estimates on all primary and secondary outcomes. All hypothesis test will be two-sided with an α of 5%. We will not adjust P-values and confidence intervals for analyses of primary or secondary outcomes. Therefore, all results for secondary outcomes should be interpreted as exploratory.

Adherence and protocol deviations

We will report the numbers and percentages of non-adherence to randomly allocated treatment.

Protocol deviations will be assessed and registered by the local coordinators at each center. Major deviations are defined as wrong inclusion (misjudgment of inclusion or exclusion criteria) or inadequate resuscitation procedures during the study period.

Analysis populations

All analyses will be conducted according to the intention-to-treat principle. Thus, patients will be analyzed in the groups that they were randomly assigned.

TRIAL POPULATION

Screening data

An active daily screening for potentially eligible patients will be performed at all the participating ICUs. Screened patients include all patients admitted to the participating ICUs with septic shock criteria or who develop these criteria during their ICU stay.[10] Patients will be either included or excluded for the study, and the reasons for these latter registered and communicated to the SSC on a weekly basis.

Eligibility

Consecutive adult patients (≥18 years) with septic shock admitted to the intensive care unit will be considered eligible. Septic shock is defined as suspected or confirmed infection, plus hyperlactatemia (≥ 2.0 mmol per liter) and vasopressor requirements due to refractory hypotension.[10] This latter is characterized as a systolic blood pressure (SBP) < 90 mmHg or a mean arterial pressure (MAP) < 65 mmHg after an intravenous fluid load of at least 20 ml/kg, administered over the course of 60 minutes.

Patients will be excluded in case of:

- pregnancy;
- anticipated surgery or dialysis procedure during the first 8 hours after septic shock diagnosis;
- Do-not-attempt-resuscitation status;
- active bleeding;
- acute hematological malignancy;
- concomitant severe acute respiratory distress syndrome (ARDS);
- more than 4h after the onset of septic shock criteria.

Recruitment

Information that will be included in the CONSORT flow diagram is shown in Fig 2.

Withdrawal/follow-up

We will tabulate the number of patients whose consent for trial participation is withdrawn either by the patient or his or her legal representative. When consent is withdrawn for trial

participation we will nevertheless attempt to obtain consent for collecting and analyzing follow-up data. These cases should also be reported.

Baseline patient characteristics

The baseline characteristics to be registered during the trial will be presented as in mock table 1.

ANALYSIS

Outcome definitions

Our primary outcome is all-cause mortality within 28 days.

Our secondary outcomes are:

- All-cause mortality within 90 days;
- Mechanical ventilation-free days during the first 28 days after randomization. A day free of mechanical ventilation is defined as no need of invasive mechanical ventilation in any time during a given day;
- Renal replacement therapy-free days during the first 28 days after randomization;
- Vasopressor-free days during the first 28 days after randomization;
- Organ dysfunction assessed with the Sepsis-related Organ Failure Assessment (SOFA) score at 72 hours after randomization;[15]
- ICU and hospital lengths of stay, truncated at 90 days;

Our tertiary exploratory outcomes are:

- Amount of resuscitation fluids in the first 8 and 24 hours after randomization;
- Total fluid balance in the first 8, 24, 48 and 72 hours;

- Occurrence of intra-abdominal hypertension (IAH) during the first 72 hours after randomization (%).
- Use of RRT (%) within 28 days;
- In-hospital mortality, truncated at 90 days.

The protocol did not call for systematic measurement of intra-abdominal pressure. Therefore, intra-abdominal pressure was measured according to physicians' discretion when they suspected of intra-abdominal hypertension.

Analysis methods

Continuous distribution will be assessed by visual inspection of histograms and D'Agostino-Pearson's normality tests. Variables will be expressed as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate, as indicated in mock tables 1 to 3, which we intend to include in the main results paper.

The evolution of hemodynamic and perfusion variables in both groups during the study will be presented as in mock table 2. We will carry out linear mixed models for continuous variables where Gaussian error distribution applies to account for the repeated measurements on the same patient. Binary variables will be tested using logistic mixed regression models and continuous variables with non-symmetrical distributions such as Lactate and Mottling score will use the distribution that best fit the data.

We will assess the effect of PPTR versus LTR on the primary outcome using Cox proportional hazards models, with adjustment for 5 pre-specified baseline covariates: APACHE II score, SOFA score, lactate level, CRT and source of infection, as fixed

(individual-level) effects. Results will be reported as hazard ratios with 95% confidence intervals (CI) and P-values. We should also present Kaplan Meier curves.

Effects on secondary and tertiary outcomes will be presented as hazard ratio for 90-day all-cause mortality and renal replacement therapy within 28 days, or risk difference for all other binary outcomes, along with 95% CI and P-values (calculated with Fisher's exact tests), as shown in mock table 3. The effect on 90-day all-cause mortality and the need of renal replacement therapy within 28 days will be assessed with Cox-proportional hazard model without adjustment for baseline covariates.

We will estimate the effect on mechanical ventilation-free days, renal replacement therapy-free days and vasopressors-free days within 28 days with generalized linear models using the distribution that better fits the data (possibly truncated Poisson distribution). Effects on organ dysfunction at 72 hours (measured by SOFA) will be calculated with generalized linear models with the distribution that better fits the data with adjustment for the baseline SOFA. Effect on other continuous outcomes, such as ICU or hospital length of stay, amount or resuscitation fluids, fluid balance, will also be calculated with generalized linear models with the distribution that better fits the data (normal, gamma, inverse Gaussian, or other), without adjustment for covariates.

Subgroup analyses

We will use Cox proportional hazards adjusted for baseline covariates (same as main analysis) to assess interactions between treatment effect and the following prespecified subgroups: a) Patients with lactate > 4.0 mmol/L versus equal or lower than 4 mmol/L; b) Patients without a confirmed source of infection (as this could increase the translation of

the study to other critically ill) versus those with confirmed source of infection; c) Patients with APACHE II lower versus equal or higher than 25; d) Patients with SOFA score lower versus equal or higher than 10; e) Patients with a more than 10% difference in lactate levels between the very first one measured and the baseline when starting the study.

Sensitivity analysis

We will assess the effect of PPTR compared to LTR on 28-day mortality using a frailty Cox model with site as random effect and adjustment for the same baseline co-variates as in the main analysis (APACHE II score, SOFA score, lactate level, CRT and source of infection).

Harms

Our primary, secondary and tertiary outcomes are intended to reflect potential harms resulting from the PPTR versus LTR approach for managing septic shocks.

Missing data

Primary outcome (28-day mortality) will be treated as time to event outcome an reported as Cox proportional hazard models, patients with loss of follow up will be censured in the last contact. We will use multiple imputation methods to assess treatment effect on the primary outcome if there are cases without no follow-up information at all. As a sensitivity analysis, we will also assess the effect on the primary outcome using complete case data.

Statistical software

Analyses will be performed using the R (R Core Team, 2017, Vienna, Austria) software.

CONCLUSION

According to the best trial practice, we report our statistical analysis plan and data

management plan prior to locking the database and starting analyses. We anticipate that this document will prevent analysis bias and enhance the utility of the reported results.

Competing interests The authors declare that they have no competing interests.

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FIGURE LEGENDS

Figure 1. Sequential approach to resuscitation. The process starts with fluid loading according to the status of fluid-responsiveness. If the goal is not obtained, the second step is a vasopressor test, and then an inodilator test.
CRT, capillary refill time; MAP, mean arterial pressure.

Figure 2. Flow of patients in the ANDROMEDA-SHOCK trial.

Table 1. Baseline Characteristics of the Patients

Characteristic	Peripheral perfusion-targeted resuscitation (n=xxx)	Lactate-targeted resuscitation (n=xxx)
Age, mean (SD), y	xx.x (xx.x)	xx.x (xx.x)
Women, no.(n%)	xxx (xx.x)	xxx (xx.x)
Charlson Comorbidity Score, median (IQR)	xx (xx to xx)	xx (xx to xx)
APACHE-II, mean (SD)	xx (xx to xx)	xx (xx to xx)
SOFA, mean (SD)	xx (xx to xx)	xx (xx to xx)
Septic shock source, no.(n%)		
Pneumonia	xxx (xx.x)	xxx (xx.x)
Urinary tract infection	xxx (xx.x)	xxx (xx.x)
Intraabdominal infection	xxx (xx.x)	xxx (xx.x)
Skin or soft-tissue infection	xxx (xx.x)	xxx (xx.x)
Other source	xxx (xx.x)	xxx (xx.x)
Infection of unknown source	xxx (xx.x)	xxx (xx.x)
Hemodynamic and perfusion-related variables		
Heart rate, mean (SD), bpm	xx.x (xx.x)	xx.x (xx.x)
Mean arterial pressure, mean (SD), mmHg	xx.x (xx.x)	xx.x (xx.x)
Norepinephrine dose, mean (SD), mcg/kg/min	x.xx (x.xx)	x.xx (x.xx)
Central venous pressure, mean (SD), mmHg	xx.x (xx.x)	xx.x (xx.x)
Serum lactate, mean (SD), mmol/L	x.xx (x.xx)	x.xx (x.xx)
Central venous oxygen saturation, mean (SD), %	xx.x (xx.x)	xx.x (xx.x)
Venous-arterial pCO2 gradient, mean (SD), mmHg	xx.x (xx.x)	xx.x (xx.x)
Capillary refilling time, median (IQR), sec	x (x to x)	x (x to x)
Mottling score, median (IQR)	x (x to x)	x (x to x)
Initial management data		
Time from matching entry criteria to randomization, mean (SD), min.	xx (xx)	xx (xx)
Intravenous fluid loading before randomization, mean SD), mL	xxxx (xxxx)	xxxx (xxxx)
Time from diagnosis of septic shock to first antibiotics, mean (SD), min.	xxx (xxx)	xxx (xxx)

Abbreviations: SD, standard deviation; IQR, interquartile range; bpm, beats per minute; SOFA, Sequential Organ Failure Assessment; APACHE, Acute physiology and chronic health evaluation.

Table 2. Evolution of Hemodynamic and Perfusion Variables from Baseline to 72 hours in the peripheral perfusion-targeted resuscitation (PPTR) and lactate-targeted resuscitation (LTR) groups

Variable	Group	Basal	2h	4h	8h	24h	48h	72h
Number of patients	PPTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	LTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Heart rate, mean, bpm	PPTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	LTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Systolic blood pressure, mean, mmHg	PPTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	LTR	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Dyastolic blood pressure, mean, mmHg	PPTR	xx	xx	xx	xx	xx	xx	xx
	LTR	xx	xx	xx	xx	xx	xx	xx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Mean arterial pressure, mean, mmHg	PPTR	xx	xx	xx	xx	xx	xx	xx
	LTR	xx	xx	xx	xx	xx	xx	xx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Norepinephrine dose, mean, mcg/Kg/min	PPTR	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	LTR	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Norepinephrine use, no. (%)	PPTR	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	LTR	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

Diuresis, mean, total mL in previous period	PPTR	-	xxx	xxx	xxx	xxx	xxx	xxx
	LTR	-	xxx	xxx	xxx	xxx	xxx	xxx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Lactate, mean, mmol/L	PPTR	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	LTR	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Capillary refill time, median, sec	PPTR	x	x	x	x	x	x	x
	LTR	x	x	x	x	x	x	x
	P-value	-	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Central venous oxygen saturation, mean, %	PPTR	xx	-	-	xx	xx	xx	xx
	LTR	xx	-	-	xx	xx	xx	xx
	P-value	-	-	-	x.xx	x.xx	x.xx	x.xx
Delta $PaCO_2$, mean, mmHg	PPTR	xx.x	-	-	xx.x	xx.x	xx.x	xx.x
	LTR	xx.x	-	-	xx.x	xx.x	xx.x	xx.x
	P-value	-	-	-	x.xx	x.xx	x.xx	x.xx
Mottling score, median	PPTR	x	-	-	x	x	x	x
	LTR	x	-	-	x	x	x	x
	P-value	-	-	-	x.xx	x.xx	x.xx	x.xx

Abbreviations: Delta $PaCO_2$, central venous-arterial pCO2 gradient

Table 3. Outcomes of Patients Treated with Peripheral Perfusion-Targeted Resuscitation versus Lactate-Targeted Resuscitation

Outcome	Peripheral perfusion-targeted resuscitation (n=xxx)	Lactate-targeted resuscitation (n=xxx)	Type of effect estimate	Effect estimate (95% CI)	P Value
Primary Outcome					
Death within 28 days, no. (n%)	xx (xx.x)	xx (xx.x)	Hazard ratio	x.xx (x.xx to x.xx)	x.xx
Secondary Outcomes					
Death within 90 days, no. (n%)	xx (xx.x)	xx (xx.x)	Hazard ratio	x.xx (x.xx to x.xx)	x.xx
Mechanical ventilation-free days within 28 days, mean (SD)	xx.x	xx.x	Mean difference	x.x (x.x)	x.xx
Renal replacement therapy-free days within 28 days, mean (SD)	xx.x	xx.x	Mean difference	x.x (x.x)	x.xx
Vasopressor-free days within 28 days, mean (SD)	xx.x	xx.x	Mean difference	x.x (x.x)	x.xx
SOFA, mean (SD)					
SOFA at 8h	x.x	x.x	Mean difference	x.x (x.x)	x.xx
SOFA at 24h	x.x	x.x	Mean difference	x.x (x.x)	x.xx
SOFA at 48h	x.x	x.x	Mean difference	x.x (x.x)	x.xx
SOFA at 72h	x.x	x.x	Mean difference	x.x (x.x)	x.xx
ICU length of stay, mean (SD), d	x.x	x.x	Mean difference	x.x (x.x)	x.xx
Hospital length of stay, mean (SD), d	x.x	x.x	Mean difference	x.x (x.x)	x.xx
Tertiary Outcomes					
Amount Resuscitation fluids, mean (SD), mL					
At 8 h	xxxx (xxxx)	xxxx (xxxx)	Mean difference	xxx (xxx to xxx)	x.xx
At 24 h	xxxx (xxxx)	xxxx (xxxx)	Mean difference	xxx (xxx to xxx)	x.xx
Total fluid balance, mean (SD), mL					
At 8 h	xxxx (xxxx)	xxxx (xxxx)	Mean difference	xxx (xxx to xxx)	x.xx
At 24 h	xxxx (xxxx)	xxxx (xxxx)	Mean difference	xxx (xxx to xxx)	x.xx
At 72 h	xxxx (xxxx)	xxxx (xxxx)	Mean difference	xxx (xxx to xxx)	x.xx

Intra-abdominal hypertension, no. (%)	xx (x.x)	xx (x.x)	Risk difference	x.x (x.x to x.x)	x.xx
Use of renal replacement therapy, no. (%)	xx (x.x)	xx (x.x)	Risk difference	x.x (x.x to x.x)	x.xx
In-hospital mortality, no. (%)	xxx (xx.x)	xxx (xx.x)	Risk difference	x.x (x.x to x.x)	x.xx

Abbreviations: SOFA, Sequential Organ Failure Assessment.