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# Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

## The ANDROMEDA-SHOCK Randomized Clinical Trial

Glenn Hernández, MD, PhD; Gustavo A. Ospina-Tascón, MD, PhD; Lucas Petri Damiani, MSc; Elisa Estenssoro, MD; Arnaldo Dubin, MD, PhD; Javier Hurtado, MD; Gilberto Friedman, MD, PhD; Ricardo Castro, MD, MPH; Leyla Alegría, RN, MSc; Jean-Louis Teboul, MD, PhD; Maurizio Cecconi, MD, FFICM; Giorgio Ferri, MD; Manuel Jibaja, MD; Ronald Pairumani, MD; Paula Fernández, MD; Diego Barahona, MD; Vladimir Granda-Luna, MD, PhD; Alexandre Biasi Cavalcanti, MD, PhD; Jan Bakker, MD, PhD; for the ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN)

**IMPORTANCE** Abnormal peripheral perfusion after septic shock resuscitation has been associated with organ dysfunction and mortality. The potential role of the clinical assessment of peripheral perfusion as a target during resuscitation in early septic shock has not been established.

**OBJECTIVE** To determine if a peripheral perfusion-targeted resuscitation during early septic shock in adults is more effective than a lactate level-targeted resuscitation for reducing mortality.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter, randomized trial conducted at 28 intensive care units in 5 countries. Four-hundred twenty-four patients with septic shock were included between March 2017 and March 2018. The last date of follow-up was June 12, 2018.

**INTERVENTIONS** Patients were randomized to a step-by-step resuscitation protocol aimed at either normalizing capillary refill time ( $n = 212$ ) or normalizing or decreasing lactate levels at rates greater than 20% per 2 hours ( $n = 212$ ), during an 8-hour intervention period.

**MAIN OUTCOMES AND MEASURES** The primary outcome was all-cause mortality at 28 days. Secondary outcomes were organ dysfunction at 72 hours after randomization, as assessed by Sequential Organ Failure Assessment (SOFA) score (range, 0 [best] to 24 [worst]); death within 90 days; mechanical ventilation-, renal replacement therapy-, and vasopressor-free days within 28 days; intensive care unit and hospital length of stay.

**RESULTS** Among 424 patients randomized (mean age, 63 years; 226 [53%] women), 416 (98%) completed the trial. By day 28, 74 patients (34.9%) in the peripheral perfusion group and 92 patients (43.4%) in the lactate group had died (hazard ratio, 0.75 [95% CI, 0.55 to 1.02];  $P = .06$ ; risk difference,  $-8.5\%$  [95% CI,  $-18.2\%$  to  $1.2\%$ ]). Peripheral perfusion-targeted resuscitation was associated with less organ dysfunction at 72 hours (mean SOFA score, 5.6 [SD, 4.3] vs 6.6 [SD, 4.7]; mean difference,  $-1.00$  [95% CI,  $-1.97$  to  $-0.02$ ];  $P = .045$ ). There were no significant differences in the other 6 secondary outcomes. No protocol-related serious adverse reactions were confirmed.

**CONCLUSIONS AND RELEVANCE** Among patients with septic shock, a resuscitation strategy targeting normalization of capillary refill time, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT03078712](https://clinicaltrials.gov/ct2/show/study/NCT03078712)

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN) members are listed at the end of this article.

**Corresponding Author:** Glenn Hernández, MD, PhD, Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Avenida Diagonal Paraguay 362, Santiago, Chile 6510260 ([glenn.guru@gmail.com](mailto:glenn.guru@gmail.com)).

**Section Editor:** Derek C. Angus, MD, MPH, Associate Editor, JAMA ([angusdc@upmc.edu](mailto:angusdc@upmc.edu)).

Early resuscitation is a key factor to limit progression to multiple organ dysfunction and death in patients with septic shock.<sup>1,2</sup> Shock is characterized by increased serum lactate levels and signs of tissue hypoperfusion including abnormal peripheral perfusion.<sup>2</sup>

Considering the strong relationship between hyperlactatemia, lactate kinetics, and mortality,<sup>3</sup> and the results of a recent study,<sup>4</sup> the Surviving Sepsis Campaign, proposes to guide hemodynamic resuscitation by repeated measurement of blood lactate levels every 2 to 4 hours until normalization.<sup>5</sup> However, persistent hyperlactatemia may be related to causes other than tissue hypoperfusion,<sup>6</sup> lactate kinetics is relatively slow even in survivors,<sup>3,7</sup> and measurements of lactate levels may not be universally available. Therefore, the exploration of alternative resuscitation targets is an important research priority in sepsis.<sup>8</sup>

Observational studies have shown that persistent abnormal peripheral perfusion after resuscitation is associated with organ failure<sup>9</sup> and mortality.<sup>10</sup> Capillary refill time (CRT) is an easy-to-use, resource-independent method to assess peripheral perfusion.<sup>11,12</sup> CRT has been shown to rapidly respond to resuscitation,<sup>7,13</sup> and its assessment might be effectively used to allow adjustments of therapy.<sup>14</sup>

Consequently, a multicenter randomized clinical trial comparing peripheral perfusion-targeted resuscitation to lactate level-targeted resuscitation in patients with early septic shock was conducted, hypothesizing that resuscitation guided by peripheral perfusion would be associated with improved outcomes.

## Methods

### Study Design and Oversight

The ANDROMEDA-SHOCK randomized clinical trial was conducted at 28 hospitals in 5 countries (Argentina, Chile, Colombia, Ecuador, Uruguay). The institutional review board at each site approved the study. Written informed consent was obtained from all patients or surrogates. The protocol and statistical analysis plan have been previously published<sup>15,16</sup> and are available in [Supplement 1](#). The trial was logistically supported by the Pontificia Universidad Católica of Chile.

The members of the steering committee designed the trial and analyzed the data. The data and safety monitoring committee oversaw the trial. The steering committee vouches for the accuracy of the data and adherence to the study protocol.

### Patient Selection and Randomization

Consecutive adult patients ( $\geq 18$  years) with septic shock admitted to the intensive care unit (ICU) were considered eligible. Septic shock was defined as suspected or confirmed infection, plus hyperlactatemia ( $\geq 2.0$  mmol/L) and requirements of vasopressors to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher after an intravenous fluid load of at least 20 mL/kg over 60 minutes.<sup>17</sup> Patients were recruited within 4 hours after fulfilling criteria. Exclusion criteria included bleeding, severe acute respiratory distress syndrome, and do-not-resuscitate status ([Supplement 1](#)).

## Key Points

**Question** Does the use of a resuscitation strategy targeting normalization of capillary refill time, compared with a strategy targeting serum lactate levels, reduce mortality among patients with septic shock?

**Findings** In this randomized clinical trial of 424 patients with early septic shock, 28-day mortality was 34.9% in the peripheral perfusion-targeted resuscitation group compared with 43.4% in the lactate level-targeted resuscitation group, a difference that did not reach statistical significance.

**Meaning** These findings do not support the use of a peripheral perfusion-targeted resuscitation strategy in patients with septic shock.

Eligible patients were randomly allocated to peripheral perfusion-targeted resuscitation (peripheral perfusion) or lactate level-targeted resuscitation (lactate) groups. A randomization sequence by permuted blocks of 8 with an allocation of 1:1 was generated by a computer program. Allocation concealment was maintained by means of central randomization. Investigators called a representative of the study coordinating center, who was available via a dedicated telephone line. Group allocation was only disclosed after the information was centrally checked and recorded.

### Study Interventions

The intervention period was 8 hours. Before starting the study, all centers were trained to assess capillary refill time with a standardized technique.<sup>15</sup> Briefly, CRT was measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure was increased until the skin was blank and then maintained for 10 seconds. The time for return of the normal skin color was registered with a chronometer, and a refill time greater than 3 seconds was defined as abnormal.

For assessment of fluid responsiveness,<sup>18</sup> each center used their standard technique when feasible and an additional algorithm was provided for difficult cases<sup>15</sup> ([Supplement 1](#)).

Lactate level was assessed every 2 hours.<sup>5</sup> CRT was evaluated every 30 minutes, because of its faster rate of recovery,<sup>7,19</sup> until normalization and then every hour during the intervention period.

The goal for the peripheral perfusion group was to normalize CRT, whereas the goal for the lactate group was to normalize or to decrease lactate levels by 20% every 2 hours.

After initial fluid resuscitation and norepinephrine to maintain a MAP of 65 mm Hg or higher, both groups were managed with an identical sequential protocolized approach to resuscitation ([eFigure 1](#) in [Supplement 2](#)).<sup>1,2</sup>

The first step was assessment of fluid responsiveness,<sup>18</sup> followed by fluid challenges with 500 mL of crystalloids every 30 minutes in fluid responders until the goal was achieved as assessed at intervals depending on the allocated group, a central venous pressure safety limit was reached,<sup>20</sup> or the patient became fluid unresponsive, whichever came first. In patients in whom fluid responsiveness could not be

determined, fluid resuscitation was continued until the goal was met or a safety limit was reached.

In patients with chronic hypertension,<sup>1,2,21</sup> if the previous interventions did not meet the goals, a vasopressor test was conducted, transiently increasing norepinephrine dose until reaching a MAP of 80 to 85 mm Hg, followed by a reassessment of CRT or lactate level after 1 or 2 hours, respectively. If the goal was met, this MAP level was maintained throughout the intervention period. Otherwise, norepinephrine was decreased to the previous dose and the patient moved to the next step, similar to patients without chronic hypertension with persistent hypoperfusion.

The third step consisted of an inodilator test with low-dose dobutamine or milrinone (depending on local protocols) if the target was still not reached.<sup>1</sup> Patients were again reassessed after 1 or 2 hours in the peripheral perfusion and lactate groups, respectively. If the end points were still not met or a safety issue arose,<sup>15</sup> the inodilator was discontinued.

A distinctive characteristic of the protocol was that when required, higher MAP targets or inodilators were introduced as a test, meaning that the effect was reassessed after a short period and the interventions maintained only in responders.

Investigators were recommended to follow Surviving Sepsis Campaign guidelines for background, refractory shock, and source control management.<sup>1</sup> Other monitoring and interventions during and after the intervention period could be used in both groups at the discretion of the attending physicians.

### Resuscitation, Perfusion, and Hemodynamic Variables

Data were collected on several perfusion and hemodynamic variables, listed in eTable 2 in [Supplement 2](#) during the first 72 hours after randomization.

### Outcome Measures

The primary outcome was all-cause mortality at 28 days. Secondary prespecified outcomes were death within 90 days; organ dysfunction during the first 72 hours after randomization (assessed by Sequential Organ Failure Assessment [SOFA] score, with higher scores indicating a greater severity of organ dysfunction in critically ill patients),<sup>22</sup> mechanical ventilation-free days within 28 days; renal replacement therapy-free days within 28 days; vasopressor-free days within 28 days; and ICU and hospital length of stay. Patients who died were assigned zero free days. Mechanical ventilation-free days, renal replacement-free days, or vasopressor-free days within 28 days were defined as the number of days alive and without use of the specific supportive therapy from randomization to day 28. Tertiary prespecified exploratory outcomes were resuscitation fluids during the intervention period; total fluid balance within 8, 24, and 72 hours; occurrence of intra-abdominal hypertension within 72 hours; use of renal replacement therapy within 28 days; and in-hospital mortality.<sup>16</sup>

A rigorous methodology was developed to reduce loss to follow-up. The true survival state at days 28 or 90 (either in or outside the hospital at that day) was determined. For patients still hospitalized at days 28 or 90, actual status was

gathered from hospital registers. Hospital mortality was truncated at the date of the database lock (June 12, 2018). For patients discharged before the critical outcome dates, follow-ups were performed by telephone calls previously announced during the informed consent process or by consulting potential death status in the national civil register or the specific health system registry, depending on the country. Electronic reminders were sent to centers before the critical dates.

Data also were collected on cases of suspected unexpected serious adverse reactions, defined as any adverse event reported by study investigators for being unexpected, serious, and having a reasonable possibility of a causal relationship with the study procedures. These reports were analyzed by the study coordinating center together with local investigators, and its relationship with the study protocol was determined.

### Statistical Analysis

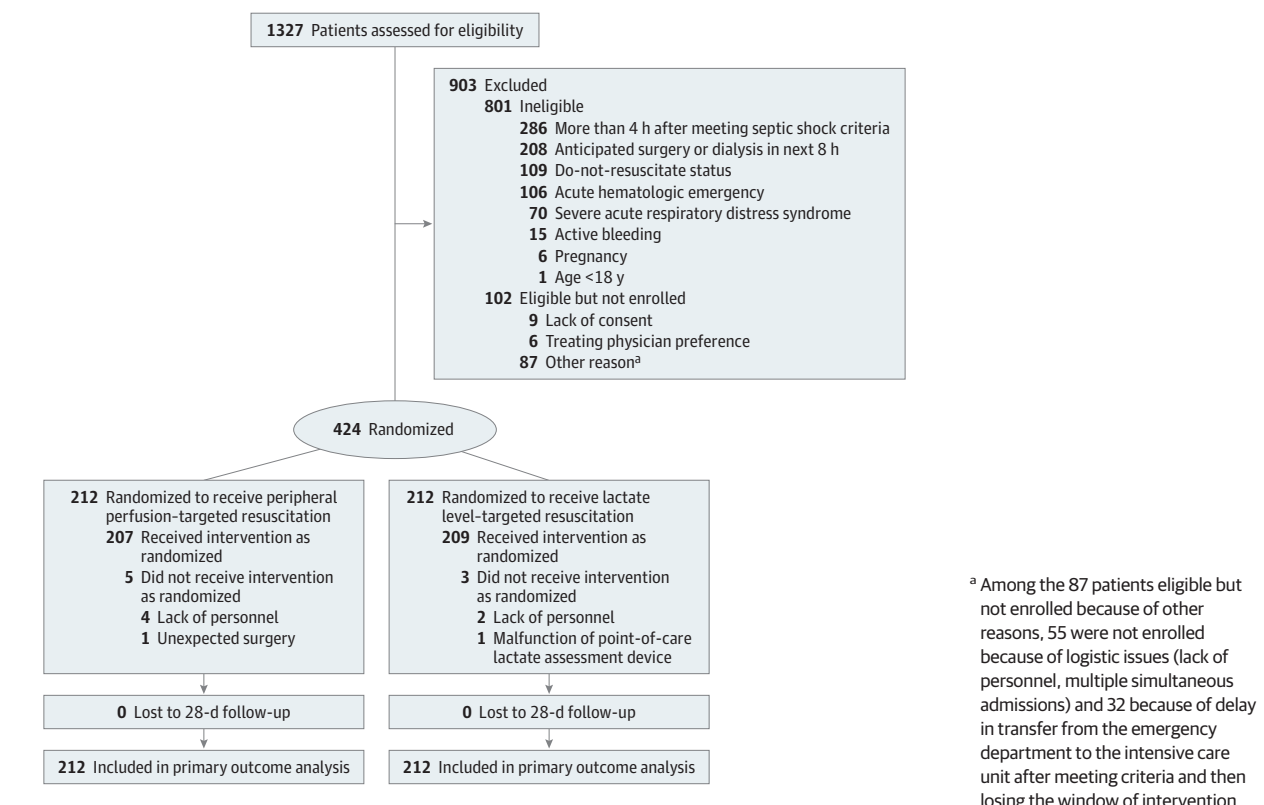
We planned to enroll 420 patients. We calculated that with this sample size the study would have 90% power to detect a reduction in 28-day mortality from 45% in the lactate group to 30% in the peripheral perfusion group,<sup>4,10,11</sup> at an  $\alpha$  level of .05. Interim analyses after the inclusion of the first 100 and 300 patients were performed by the data and safety monitoring committee, which had no preestablished formal stopping rules. After both analyses the committee recommended to continue the trial without alterations.

We compared resuscitation, perfusion, and hemodynamic categorical variables between treatment groups with Fisher exact tests. For continuous variables, generalized linear mixed models with different distributions were used: Gaussian distribution was used for heart rate, central venous oxygen saturation, and systolic, diastolic, and mean arterial blood pressures; gamma distribution was used for norepinephrine dose, diuresis, lactate level, CRT, and central venous-arterial  $\text{PCO}_2$  gradient; binomial (logistic model) was used for norepinephrine use.

The treatment effect on the primary outcome was calculated with Cox proportional hazards, with adjustment for 5 prespecified baseline covariates: Acute Physiology and Chronic Health Evaluation (APACHE) II score,<sup>23</sup> SOFA score,<sup>24</sup> lactate level, CRT, and source of infection. The proportional hazards assumption was tested with the Grambsch and Therneau method.<sup>25</sup> Results are reported as hazard ratio with 95% confidence interval and as Kaplan-Meier curves.

The effect on 90-day all-cause mortality was assessed with Cox proportional hazards model. Other binary secondary and tertiary outcomes were tested using Fisher exact tests. Treatment effect on mechanical ventilation-free days, renal replacement therapy-free days, and vasopressor-free days within 28 days was analyzed by zero-inflated negative binomial models. ICU and hospital length of stay and resuscitation fluids were assessed with generalized linear models with gamma distribution. Fluid balance was compared with linear regression. The treatment effect on organ dysfunction at 72 hours was evaluated with linear regression adjusting

Figure 1. Flow of Participants Through the Study



for baseline SOFA score. As a post hoc analysis, we compared SOFA values measured during the 72 hours (at 8, 24, 48, and 72 hours) between treatment groups using a mixed linear regression model, with adjustment for baseline SOFA score, considering time as a continuous variable, patient as random effect, and a treatment  $\times$  time interaction term. Analyses of secondary or tertiary outcomes were not adjusted for covariates.

A prespecified sensitivity analysis was performed using a frailty Cox model with sites as random effects, assuming a gamma distribution, adjusted for the same covariates as in the main model—results were presented as marginal effects. Frailty models account for the possible heterogeneity of treatment effects across trial sites. Subgroup analyses, with Cox proportional hazards adjusted for the same covariates as in the main model, were conducted to assess interactions between treatment effect and the following prespecified baseline characteristics: lactate levels ( $>4.0$  vs  $\leq 4.0$  mmol/L); APACHE II score ( $<25$  vs  $\geq 25$ ); SOFA score ( $<10$  vs  $\geq 10$ ); source of infection (confirmed vs unconfirmed); variation of lactate level between first measurement and baseline measurement ( $\geq 10\%$  vs  $<10\%$ ).<sup>16</sup> Several additional post hoc sensitivity analyses listed in the eMethods in Supplement 2, including per protocol analyses, were performed. Furthermore, in a post hoc analysis, we assessed whether treatment effect on the primary outcome might differ across sites using a Cox proportional hazards

model adjusted for the same covariates as the main model and a treatment  $\times$  site interaction term.

Patients were analyzed according to randomization group, except when indicated otherwise. All hypothesis tests were 2-sided, with a significance level of .05 and no adjustments for the interim analyses, multiple outcomes, or subgroup analyses. Therefore, analyses of secondary outcomes and other outcomes should be considered exploratory. Analyses were conducted using R version 3.4.1 (R Core Team).

## Results

### Patients

From March 2017 through March 2018, 1327 patients were assessed for eligibility (Figure 1). A total of 424 patients were enrolled (mean age, 63 years; 226 [53%] women), with 212 assigned to each group (Figure 1; eFigure 2 and eTable 1 in Supplement 2). Data for the primary and secondary outcomes were obtained for all patients. All patients were included in the intention-to-treat analysis for the primary outcome.

Baseline patient characteristics were similar (Table 1). Seventy-one percent of the patients were admitted from the emergency department, 17% from wards, 7% from step-down units, and 5% directly from the operating room.

Table 1. Patient Characteristics at Baseline<sup>a</sup>

Characteristic	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)
Age, mean (SD), y	62 (17)	64 (17)
Sex, No. (%)		
Men	108 (50.9)	90 (42.5)
Women	104 (49.1)	122 (57.5)
Charlson Comorbidity Index, median (IQR) <sup>b</sup>	3 (1-5)	3 (1-5)
APACHE II, mean (SD) <sup>c</sup>	21.9 (8.0)	22.0 (7.6)
SOFA, mean (SD) <sup>d</sup>	9.7 (3.4)	9.6 (3.5)
Chronic hypertension, No. (%)	83 (39.2)	93 (43.9)
Confirmed microbiology, No. (%)	151 (71.2)	153 (72.2)
Septic shock source, No. (%)		
Intra-abdominal infection	72 (34.0)	77 (36.3)
Pneumonia	70 (33.0)	58 (27.4)
Urinary tract infection	42 (19.8)	45 (21.2)
Other sources <sup>e</sup>	18 (8.5)	19 (9.0)
Unknown origin	10 (4.7)	13 (6.1)
Hemodynamic and perfusion-related variables		
Heart rate, mean (SD), /min	103 (24)	104 (23)
Arterial blood pressure, mean (SD), mm Hg	69 (14)	68 (13)
Norepinephrine dose, median (IQR), µg/kg/min	0.24 (0.11-0.40)	0.20 (0.10-0.35)
Central venous pressure, No.	199	194
Median (IQR), mm Hg	9 (6-13)	9 (6-12)
Serum lactate, mean (SD), mmol/L	4.6 (4.3)	4.5 (2.5)
Central venous oxygen saturation, No.	204	197
Mean (SD)	71 (13)	71 (12)
Venous-arterial Pco <sub>2</sub> gradient, No.	203	195
Median (IQR), mm Hg	7 (5-10)	7 (5-10)
Capillary refill time		
Median (IQR), s	5 (4-6)	4 (3-6)
≤3 s, No. (%)	48 (22.6)	60 (28.3)
Initial management data, median (IQR)		
Time from matching entry criteria to randomization, h	1.5 (0.0-3.0)	1.3 (0.0-2.6)
Intravenous fluid loading per weight, mL/kg <sup>f</sup>	25 (16-40)	30 (20-43)
Time from diagnosis of septic shock to antibiotics, h	2.0 (1.0-2.0)	1.5 (1.0-2.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

<sup>a</sup> For variables with missing data, summary data are based on available cases.

<sup>b</sup> Range, 0 to 33; higher scores indicate a greater burden of disease.

<sup>c</sup> Range, 0 to 71; higher scores indicate greater severity of illness and risk of in-hospital death (eg, a score of 22 in a medical patient with sepsis predicts an in-hospital mortality of 45%).<sup>22</sup>

<sup>d</sup> Range, 0 to 24; higher scores indicate a greater severity of organ dysfunction in critically ill patients and risk of in-hospital death (eg, a score of 10 predicts an in-hospital mortality of 50%).<sup>22</sup>

<sup>e</sup> Other sources of infection were soft-tissue infection (n = 18), meningitis (n = 6), central line-associated bloodstream infection (n = 4), endocarditis (n = 2), mediastinitis (n = 2), herpes encephalitis (n = 1), subdural empyema (n = 1), pleural empyema (n = 1), septic arthritis (n = 1), and septic abortion (n = 1).

<sup>f</sup> Total intravenous fluids include fluids administered during the interval between presentation to the emergency department and randomization.

### Adherence to the Protocol

Lack of adherence was registered in 29 patients (13.7%) in the peripheral perfusion group and 23 (10.8%) in the lactate group (eTable 3 in Supplement 2). Most of these instances were protocol deviations (26 in the peripheral perfusion group and 20 in the lactate group), and 8 patients did not receive the assigned intervention. Protocol deviations were protocol mismanagement in 16 instances in each group, and early termination of assigned treatment for refractory shock in 8 instances in the peripheral perfusion group and 4 instances in the lactate group.

### Resuscitation, Perfusion, and Hemodynamic Variables

Two-hundred forty-two patients (57%) were fluid responsive and 106 (25%) fluid unresponsive at baseline, without differences between groups. Fluid responsiveness could not be determined in 76 patients (18%). The most frequently used techniques were pulse pressure variation and passive leg raising with velocity time integral determination in 144 patients in each group. Evolution of fluid responsiveness during the intervention period is shown in eFigure 3 in Supplement 2.

Fewer patients in the peripheral perfusion group (28.8%) than in the lactate group (40.1%) required a vasopressor test

(difference, -11.3% [95% CI, -20.8% to -1.9%];  $P = .02$ ) (eTable 4 in [Supplement 2](#)), although success was not different (44% vs 38%, respectively;  $P = .86$ ). Sixty-six of the patients (15.6%) received inodilators, without any significant difference between groups.

When considering the whole group of 424 patients independently of fluid responsiveness status, lactate levels were significantly lower at 48 hours and 72 hours in the peripheral perfusion group than in the lactate group (mean difference, -0.36 mmol/L [95% CI, -0.62 to -0.09];  $P = .01$  in the peripheral perfusion group vs -0.34 mmol/L [95% CI, -0.57 to -0.10] in the lactate group;  $P < .01$ ), although there were no statistically significant differences at 2, 4, 8, and 24 hours (eTable 2 in [Supplement 2](#)). CRT values were significantly lower at 4, 8, and 24 hours in the peripheral perfusion group compared with the lactate group (difference between medians, -0.45 seconds [95% CI, -0.78 to -0.12];  $P = .01$  at 4 hours, -0.55 [95% CI, -0.85 to -0.25];  $P < .01$  at 8 hours, -0.42 [95% CI, -0.71 to -0.13];  $P < .01$  at 24 hours), with no statistically significant differences at 2, 48, and 72 hours. Evolution of CRT and lactate levels exclusively in fluid unresponsive patients is shown in eTable 5 in [Supplement 2](#).

Central venous oxygen saturation and central venous-arterial  $\text{PCO}_2$  gradients were not significantly different between groups (eTable 2 and eFigure 4 in [Supplement 2](#)). Other parameters are shown in eTable 2 in [Supplement 2](#).

### Primary Outcome

By day 28, a total of 74 patients (34.9%) in the peripheral perfusion group and 92 (43.4%) in the lactate group had died (hazard ratio, 0.75 [95% CI, 0.55 to 1.02];  $P = .06$ ; risk difference, -8.5% [95% CI, -18.2% to 1.2%]) (Table 2 and Figure 2). There was no evidence of violation of the proportional hazards assumption (Grambsch and Therneau test  $P = .07$ ).

### Secondary and Tertiary Outcomes

There was significantly less organ dysfunction at 72 hours after randomization in the peripheral perfusion group (mean difference in SOFA score, -1.00 [95% CI, -1.97 to -0.02];  $P = .045$ ) (Table 2). There were no significant between-group differences in the other 6 secondary outcomes (Table 2).

Patients in the peripheral perfusion group received less resuscitation fluids within the first 8 hours (mean difference, -408 mL [95% CI, -705 to -110];  $P = .01$ ) (Table 2).

Twelve cases of suspected unexpected serious adverse reactions were reported by centers, without differences between groups, but none was considered as likely related to the study protocol.

### Subgroup and Sensitivity Analyses

Results of the prespecified subgroup analysis are reported in Figure 3. Treatment effect on the primary outcome was heterogeneous according to baseline SOFA subgroups ( $P = .03$  for interaction). Among patients with SOFA score less than 10, the hazard ratio for 28-day mortality was 0.46 (95% CI, 0.27 to 0.78), whereas among patients with SOFA

score 10 or greater the hazard ratio was 0.98 (95% CI, 0.66 to 1.44). There were no significant differences in treatment effect in the other prespecified subgroup analyses. There was also no evidence of heterogeneity of treatment effects across sites (eFigure 5 in [Supplement 2](#)). Estimates of treatment effect on 28-day mortality from the prespecified sensitivity analysis (frailty Cox model) were similar to those from the main analysis.

### Post Hoc Analysis

Estimates of treatment effect for several post hoc sensitivity analyses, including per protocol analyses, were also similar to the main analysis (eTable 6 in [Supplement 2](#)). There was no evidence of heterogeneity of treatment effects across sites (eFigure 5 in [Supplement 2](#)). In a post hoc analysis considering all SOFA measurements during the first 72 hours, there was significantly less organ dysfunction among patients in the peripheral perfusion group compared with the lactate group (mean difference, -1.16 [95% CI, -1.96 to -0.36];  $P = .01$ ) (Figure 4).

## Discussion

In this multicenter randomized clinical trial involving patients with early septic shock, a peripheral perfusion-targeted resuscitation strategy did not result in a significantly lower 28-day mortality when compared with a lactate level-targeted strategy.

The study protocol operationalized, in a stepwise fashion, interventions for septic shock resuscitation widely recommended by current guidelines<sup>1,5</sup> or consensus/expert recommendations.<sup>2,26</sup> The small but significant differences found in some protocol-related interventions suggest that targets were actively pursued according to the assigned group. The protocol was applied in a context of heterogeneous multinational ICUs with few registered violations, but its potential generalizability requires further studies.

Fluid administration was based on fluid responsiveness status during the intervention period<sup>15</sup> and directed by repeated evaluation of the respective assigned targets. In this sense, peripheral perfusion-targeted resuscitation resulted in a small but significant difference in resuscitation fluids, which is consistent with recent observations<sup>14</sup> and could merit further exploration in the context of increasing awareness of the risks of fluid overload. In contrast to previous studies,<sup>27</sup> fluid responsiveness was determined in more than 80% of the patients. The participation of only highly committed centers with experience in assessment of fluid responsiveness might have contributed to this.

Increasing MAP to levels of 80 to 85 mm Hg in patients with chronic hypertension has been recommended by recent guidelines and expert opinions.<sup>1,2</sup> This recommendation was operationalized in the vasopressor test when CRT or lactate targets were not reached. The increase in MAP resulted in the achievement of the respective resuscitation target in about 40% of patients in both study groups. These results could provide a basis for further exploring the use of

Table 2. Main Outcomes of the Study of Resuscitation Strategies in Septic Shock

Outcome	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)	Unadjusted Absolute Difference (95% CI)	Adjusted Relative Measure (95% CI)	P Value
<b>Primary Outcome</b>					
Death within 28 d, No. (%)	74 (34.9)	92 (43.4)	-8.5 (-18.2 to 1.2) <sup>b</sup>	HR, 0.75 (0.55 to 1.02) <sup>a</sup>	.06 <sup>a</sup>
<b>Secondary Outcomes</b>					
Death within 90 d, No. (%)	87 (41.0)	99 (46.7)	-5.7 (-15.6 to 4.2) <sup>b</sup>	HR, 0.82 (0.61 to 1.09) <sup>a</sup>	.17 <sup>a</sup>
Mechanical ventilation-free days within 28 d, mean (SD) <sup>c</sup>	14.6 (12.1)	12.7 (12.2)	1.9 (-0.6 to 4.3)		.14
Renal replacement therapy-free days within 28 d, mean (SD) <sup>c</sup>	18.5 (12.1)	16.9 (12.1)	1.7 (-1.5 to 4.8)		.31
Vasopressor-free days within 28 d, mean (SD) <sup>c</sup>	16.7 (12.0)	15.1 (12.3)	1.6 (-0.7 to 3.9)		.18
SOFA at 72 h, No. <sup>d</sup>	165	166			.045
Mean (SD)	5.6 (4.3)	6.6 (4.7)	-1.00 (-1.97 to -0.02)		
ICU length of stay, mean (SD), d <sup>e</sup>	9.1 (9.8)	9.0 (9.6)	0.1 (-1.7 to 2.0)		.91
Hospital length of stay, mean (SD), d <sup>f</sup>	22.9 (28.8)	18.3 (19.0)	4.6 (0.0 to 9.1)		.05
<b>Exploratory Outcomes</b>					
Amount of resuscitation fluids within the first 8 h, No.	206	209			
Mean (SD), mL	2359 (1344)	2767 (1749)	-408 (-705 to -110)		.01
<b>Total fluid balance, mL<sup>g</sup></b>					
Within 8 h, No.	198	205			
Mean (SD)	1587 (1388)	1874 (1756)	-288 (-598 to 22.0)		.07
Within 24 h, No.	176	185			
Mean (SD)	2025 (2181)	2343 (2336)	-318 (-785 to 149)		.18
Within 48 h, No.	153	160			
Mean (SD)	992 (1810)	1224 (3336)	-233 (-831 to 366)		.45
Within 72 h, No.	157	162			
Mean (SD)	1389 (2809)	1601 (3069)	-212 (-858 to 434)		.52
Intra-abdominal hypertension, No. of events/total (%) <sup>h</sup>	75/119 (63.0)	68/120 (56.7)	6.4 (-6.9 to 19.6)	RR, 1.11 (0.90 to 1.37)	.36 <sup>i</sup>
Use of renal replacement therapy, No. (%)	30 (14.2)	42 (19.8)	-5.7 (-13.3 to 1.9)	RR, 0.71 (0.47 to 1.10)	.15 <sup>i</sup>
In-hospital mortality, No. (%)	84 (39.6)	97 (45.8)	-6.1 (-16.0 to 3.7)	RR, 0.87 (0.69 to 1.08)	.20 <sup>i</sup>

Abbreviations: HR, hazard ratio; ICU, intensive care unit; RR, risk ratio; SOFA, Sequential Organ Failure Assessment.

<sup>a</sup> Hazard ratio (95% CI) and *P* value calculated with Cox proportional hazards model with adjustment for baseline values of Acute Physiology and Chronic Health Evaluation II score, SOFA score, lactate levels, capillary refill time, and source of infection.

<sup>b</sup> Absolute difference (95% CI) calculated from Cox proportional hazard model without adjustment for covariates.

<sup>c</sup> Treatment effects on mechanical ventilation, renal replacement therapy, and vasopressor use assessed with zero inflated negative binomial models.

<sup>d</sup> Treatment effect calculated with linear regression adjusting for baseline SOFA score.

<sup>e</sup> Treatment effects on ICU stay, hospital stay, and resuscitation fluids assessed with generalized linear models with gamma distribution.

<sup>f</sup> Patients still in the hospital for 90 days or more after randomization were considered to be discharged alive at day 90.

<sup>g</sup> Fluid balance within 8, 24, and 72 hours was calculated as all intravenous fluids minus urine output and gastrointestinal losses from randomization to the specified time point. Treatment effect on total fluid balance was calculated with linear regression.

<sup>h</sup> Defined as an intra-abdominal pressure equal or higher than 12 mm Hg. Intra-abdominal pressure was measured via the bladder, with instillation of 25 mL of sterile saline at end-expiration in the complete supine position, with transducer zeroed at the level of the mid-axillary line.

<sup>i</sup> From Fisher exact test.

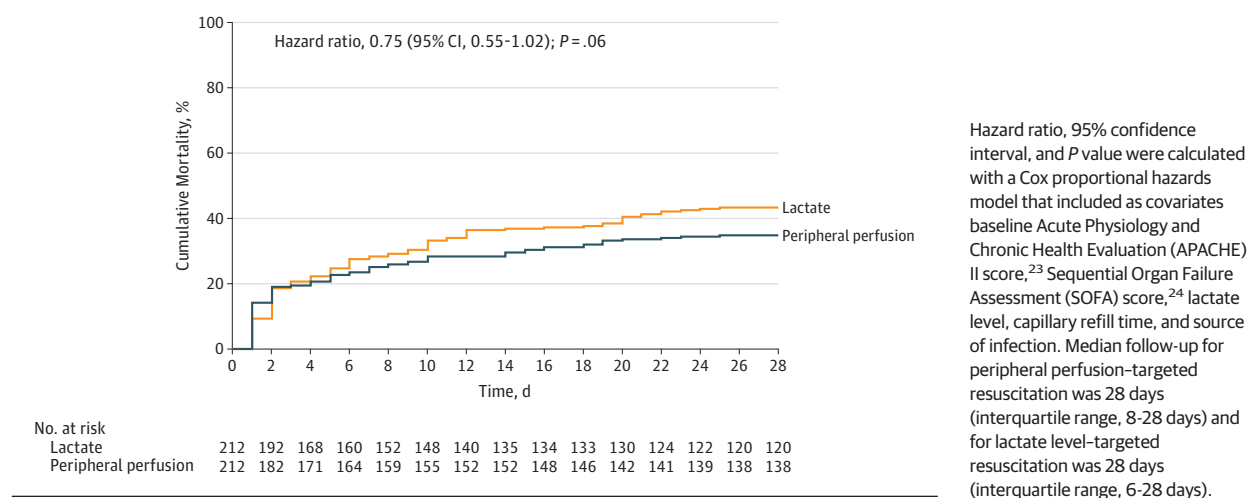
higher MAP targets in patients with septic shock and a history of chronic hypertension.

Peripheral perfusion-targeted resuscitation was associated with beneficial effects on the secondary outcome of SOFA score at 72 hours and lower 28-day mortality in the predefined subgroup of patients with less severe organ dysfunction at baseline. These results are in line with those from some observational studies that showed that normalization of peripheral perfusion after initial resuscitation

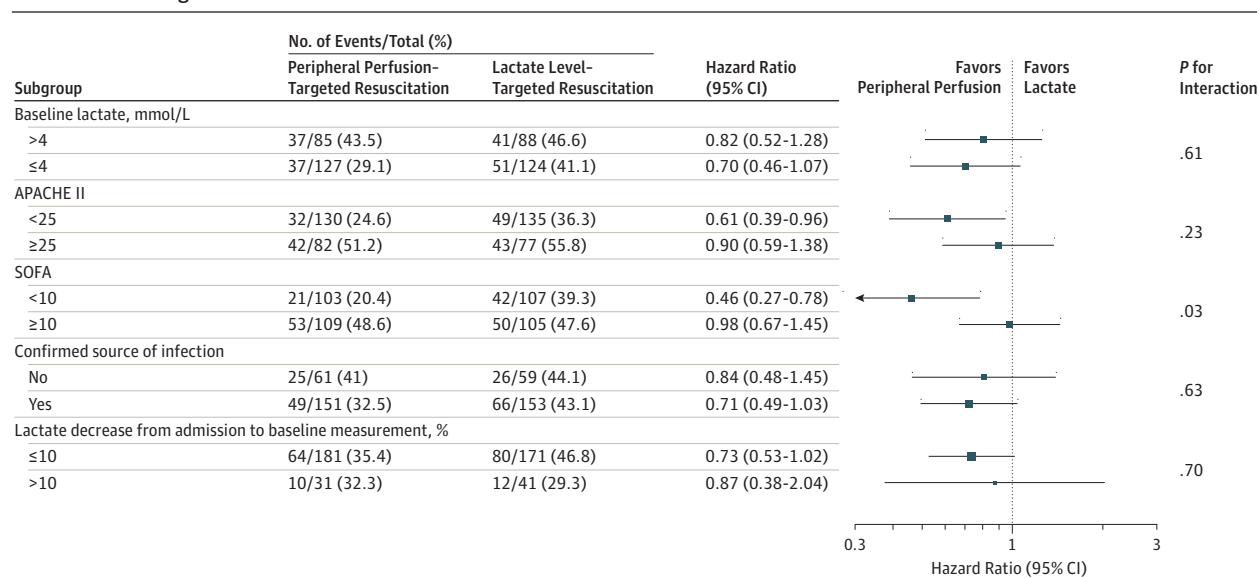
was associated with lower mortality and less organ dysfunction<sup>9-11</sup> and from a pilot study that suggested that restriction of fluid resuscitation based on normal peripheral perfusion was associated with improvement in organ dysfunction.<sup>14</sup> Because of the exploratory nature of such secondary outcomes and analyses, these findings should be confirmed by further research.

The use of CRT in clinical practice is not devoid of problems. CRT is dependent on age, sex, ambient temperature

**Figure 2. Kaplan-Meier Estimates of Cumulative Mortality Within 28 Days Among Patients Treated With Peripheral Perfusion-Targeted Resuscitation vs Lactate Level-Targeted Resuscitation**



**Figure 3. Risk of Death Within 28 Days in the Prespecified Subgroups Among Patients Treated With Peripheral Perfusion-Targeted Resuscitation vs Lactate Level-Targeted Resuscitation**



The area of the square representing the hazard ratio is proportional to the number of events in each subgroup. Horizontal bars represent 95% CI. *P* values are for heterogeneity of treatment effect on the primary outcome in each subgroup. Hazard ratios and 95% CIs were calculated with Cox proportional hazards model adjusted for the baseline covariates Acute Physiology and

Chronic Health Evaluation (APACHE) II score,<sup>23</sup> Sequential Organ Failure Assessment (SOFA) score,<sup>24</sup> lactate level, capillary refill time, and source of infection. *P* values were calculated with treatment × subgroup interaction terms. See Table 1 notes for APACHE II and SOFA definitions.

and light, and pressure applied during the maneuver—all factors that might influence results.<sup>28-30</sup> Although no relationship between CRT and hypovolemia was found in older studies,<sup>31</sup> more recent studies performed in critically ill patients, including those with septic shock, have shown clinically relevant associations with outcome.<sup>9-11,19,32</sup> More importantly, CRT was used as a measure of tissue perfusion rather than a surrogate for macrohemodynamics.

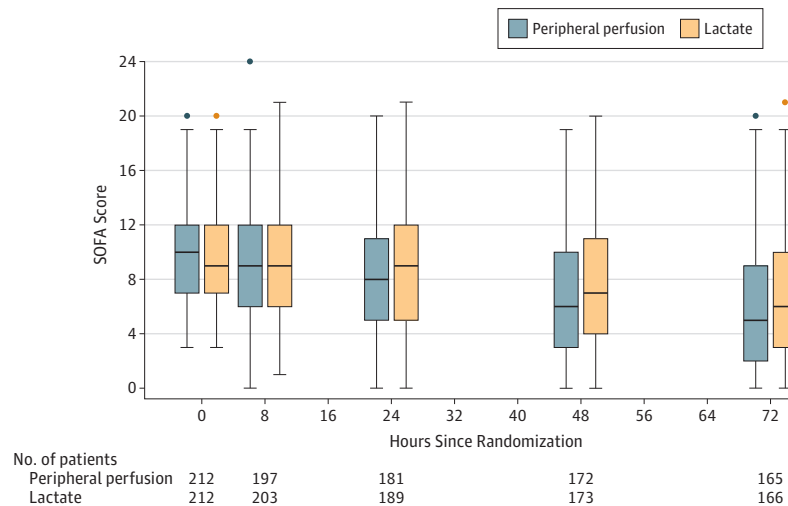
The issue of interrater reliability is controversial.<sup>33</sup> However, objective CRT measurements obtained by trained ICU

physicians using a chronometer revealed good interrater reliability,<sup>11,12</sup> contrasting with unreliable observations when CRT was subjectively measured.<sup>34</sup> To reduce inaccuracies, a standardized procedure adopting a CRT of 3 seconds as normal was used according to recent clinical observations.<sup>11</sup>

### Limitations

This study has several limitations. First, the nonblinded design might have introduced bias. However, a primary outcome not subject to observer bias was used. In addition,

Figure 4. Organ Dysfunction During the First 72 Hours After Randomization Among Patients Treated With Peripheral Perfusion-Targeted Resuscitation vs Lactate Level-Targeted Resuscitation



This post hoc analysis is a mixed linear regression considering patient as random effect and adjusting for baseline Sequential Organ Failure Assessment (SOFA) score.  $P < .001$  for mean SOFA score treatment  $\times$  time interaction within 72 hours. Organ dysfunction assessed by SOFA score<sup>23</sup> at baseline and 8, 24, 48, and 72 hours after randomization. SOFA scores range from 0 to 24, with higher

scores indicating a greater severity of organ dysfunction and risk of death.<sup>23</sup> Box plots indicate 75th percentile (top edge of box), 25th percentile (bottom edge of box), and 50th percentile (bold horizontal line in box); whiskers indicate minimum and maximum values up to 1.5 times the interquartile range from the quartiles; circles indicate values that exceed 1.5 times the interquartile range.

several measurements were taken to minimize potential cross-treatments, including intensive training, auditing, and periodic reinforcement of the study procedures. At the end, adherence and major violations were not different between groups (eTable 3 in Supplement 2). Second, the study may have been underpowered to exclude a clinically meaningful difference between groups. In fact, this is the first major interventional trial testing the potential role of CRT as a resuscitation target, and therefore no previous data to facilitate a power calculation were available. Thus, the estimated effect of peripheral perfusion-targeted resuscitation and the sample size calculation were based mainly on small observational studies and might have been subject to error. Third, interrater variability for CRT was not evaluated; nevertheless, personnel at all centers were thoroughly trained to assess CRT using a standardized technique. Fourth, randomization was not stratified by sites. Therefore, imbalances in the allocation to the treatment groups within sites may have

occurred by chance. However, this may have a small or null effect on the effect estimates, since the results of the sensitivity analysis with the frailty Cox model, which consider within-site effects, were consistent with those from the main analysis. Fifth, while the protocol used might appear complex, it only operationalizes interventions widely recommended by current guidelines into a stepwise protocol. Sixth, since this was an ICU-based study, it does not provide information on how effective this approach might be in other contexts, such as wards or resource-limited settings.

## Conclusions

Among patients with septic shock, a resuscitation strategy targeting normalization of capillary refill time, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality.

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**Author Affiliations:** Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago (Hernández, Castro, Alegría, Bakker); Fundación Valle del Lili, Universidad ICESI, Department of Intensive Care Medicine, Cali, Colombia (Ospina-Tascón); HCor Research Institute–Hospital do Coração, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil (Damiani, Cavalcanti); Hospital Interzonal de Agudos San Martín de La Plata, La Plata, Argentina (Estenssoro); Sanatorio

Otamendi, Buenos Aires, Argentina (Dubin); Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, La Plata, Argentina (Dubin); Intensive Care Unit, Hospital Español-ASSE, Montevideo, Uruguay (Hurtado); Department of Pathophysiology, School of Medicine Universidad de la República, Montevideo, Uruguay (Hurtado); Post-Graduation Program in Pneumological Sciences, Department of Internal Medicine, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (Friedman); Service de Réanimation Médicale, Hôpital Bicêtre, Hôpitaux Universitaires Paris-Sud, Paris, France (Teboul); Assistance Publique Hôpitaux de Paris, Université Paris-Sud, Paris, France (Teboul); Humanitas Clinical and

Research Center, Department of Biomedical Sciences, Humanitas University, Milan, Italy (Cecconi); Unidad de Cuidados Intensivos, Hospital Barros Luco Trudeau, Santiago, Chile (Ferri, Pairumani); Unidad de Cuidados Intensivos, Hospital Eugenio Espejo, Escuela de Medicina, Universidad Internacional del Ecuador, Quito (Jibaja); Unidad de Pacientes Críticos, Hospital Guillermo Grant Benavente, Concepción, Chile (Fernández); Unidad de Cuidados Intensivos, Hospital General Docente de Calderón, Universidad Central del Ecuador, Quito (Barahona); Unidad de Cuidados Intensivos, Hospital San Francisco, Pontificia Universidad Católica de Quito, Quito, Ecuador (Granda-Luna); Department of Intensive Care Adults, Erasmus MC University Medical Center,

Rotterdam, the Netherlands (Bakker); Department of Pulmonary and Critical Care, New York University, New York, New York (Bakker); Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, New York (Bakker).

**Author Contributions:** Drs Hernández and Bakker had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Hernández and Bakker contributed equally to this article.

**Concept and design:** Hernández, Ospina-Tascón, Teboul, Biasi Cavalcanti, Bakker.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Hernández, Ospina-Tascón, Petri Damiani, Estenssoro, Teboul, Biasi Cavalcanti, Bakker.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Petri Damiani, Biasi Cavalcanti.

**Obtained funding:** Hernández.

**Administrative, technical, or material support:** Hernández, Castro, Alegría, Ferri.

**Supervision:** Hernández, Castro, Alegría, Bakker.

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**The ANDROMEDA-SHOCK and the Latin America Intensive Care Network (LIVEN) Investigators:**

**Writing and Steering Committee:** Glenn Hernández (cochair), Gustavo Ospina-Tascón, Lucas Petri Damiani, Elisa Estenssoro, Arnaldo Dubin, Javier Hurtado, Gilberto Friedman, Ricardo Castro, Leyla Alegría, Jean-Louis Teboul, Maurizio Cecconi, Giorgio Ferri, Manuel Jibaja, Ronald Pairumani, Paula Fernández, Diego Barahona, Alexandre Biasi Cavalcanti, Jan Bakker (cochair). **Study**

**Coordinating Center:** Glenn Hernández, Leyla Alegría, Giorgio Ferri, Nicolás Rodríguez, Patricia Holger, Natalia Soto, Mario Pozo, Jan Bakker. **Data and Safety Monitoring Committee:** Deborah Cook, Jean-Louis Vincent, Andrew Rhodes, Bryan P. Kavanagh, Phil Dellinger, Wim Rietdijk (statistician).

**Latin America Intensive Care Network (LIVEN):**

**Chile:** Pontificia Universidad Católica de Chile, Santiago (David Carpio, Nicolás Pavéz, Elizabeth Henríquez, Sebastian Bravo, Emilio Daniel Valenzuela, Magdalena Vera, Jorge Dreyse, Vanessa Oviedo); Hospital Barros-Luco Trudeau, Santiago (María Alicia Cid, Macarena Larroulet, Edward Petruska, Claudio Sarabia); Hospital San Juan de Dios, Santiago (David Gallardo, Juan Eduardo Sanchez, Hugo González, José Miguel Arancibia, Alex Muñoz, Germán Ramírez, Florencia Aravena); Hospital Dr Sótero del Río, Santiago (Andrés Aquevedo, Fabián Zambrano); Hospital Del Salvador, Santiago (Milan Bozinovic, Felipe Valle,

Manuel Ramírez, Víctor Rossel, Pilar Muñoz, Carolina Ceballos); Hospital Herminda Martínez, Chillán (Christian Esveile, Cristian Carmona, Eva Candia, Daniela Mendoza); Hospital San Juan de Dios, Curicó (Aída Sánchez); Hospital Guillermo Grant Benavente, Concepción (Daniela Ponce, Jaime Lastra, Bárbara Nahuelpán, Fabrizio Fasce); Hospital Clínico Universidad de Chile, Santiago (Cecilia Luengo, Nicolas Medel, Cesar Cortés). **Argentina:** Clínica La Pequeña Familia, Junín (Luz Campassi); Sanatorio Otamendi y Miroli, Buenos Aires (Paolo Rubatto, Brenda Nahime Horna, Mariano Furche); Hospital Provincial del Centenario, Rosario (Juan Carlos Pendino, Lisandro Bettini); Sanatorio Parque, Rosario (Carlos Lovesio, María Cecilia González, Jéssica Rodríguez); Hospital Interzonal San Martín, La Plata (Héctor Canales, Francisco Caminos); Sanatorio Allende Nueva Córdoba (Cayetano Galletti, Estefanía Minoldo, María José Aramburu, Daniela Olmos); **Uruguay:** Hospital Español Juan J Crotogini, Montevideo (Nicolás Nin, Jordán Tenzi, Carlos Quiroga, Pablo Lacuesta, Agustín Gaudín, Richard Pais, Ana Silvestre, Germán Olivera); Hospital de Clínicas, Montevideo (Gloria Rieppi, Dolores Berrutti). **Ecuador:** Hospital Universitario del Río, Cuenca (Marcelo Ochoa, Paul Cobos, Fernando Vintimilla); Hospital Eugenio Espejo, Quito (Vanessa Ramírez, Milton Tobar, Fernanda García, Fabricio Picoita, Nelson Remache); Hospital San Francisco, Quito (Vladimir Granda, Fernando Paredes, Eduardo Barzallo, Paul Garcés); Hospital Carlos Andrade Marín, Quito (Fausto Guerrero, Santiago Salazar, German Torres, Cristian Tana, José Calahorrano, Freddy Solís); Hospital IESS, Ibarra (Pedro Torres, Luis Herrera, Antonio Ornes, Verónica Peréz, Glenda Delgado, Alexei López, Eliana Espinosa, José Moreira); Hospital General Docente Calderón, Quito (Blanca Salcedo, Ivonne Villacres, Jhonny Suing, Marco Lopez, Luis Gomez, Guillermo Toctaquiza, Mario Cadena Zapata, Milton Alonso Orazabal, Ruben Pardo Espejo, Jorge Jimenez, Alexander Calderón); Hospital Enrique Garcés, Quito (Gustavo Paredes, José Luis Barberán, Tatiana Moya). **Colombia:** Hospital San Vicente de Paul, Medellín (Horacio Atehortua, Rodolfo Sabogal); Hospital de Santa Clara, Bogotá (Guillermo Ortiz, Antonio Lara); Hospital Universitario de Nariño E.S.E., Pasto (Fabio Sanchez, Alvaro Hernán Portilla, Humberto Dávila, Jorge Antonio Mora); Fundación Valle del Lili, Cali (Luis Eduardo Calderón, Ingrid Alvarez, Elena Escobar, Alejandro Bejarano, Luis Alfonso Bustamante, José Luis Aldana).

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