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Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock
The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

The ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN)

IMPORTANCE The optimal strategy for hemodynamic resuscitation in early septic shock remains uncertain.

OBJECTIVE To determine the effect of a personalized hemodynamic resuscitation protocol targeting capillary refill time (CRT-PHR) on a hierarchical composite outcome of mortality, duration of vital support, and length of hospital stay.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial was conducted in 86 centers in 19 countries. Patients within the first 4 hours of septic shock were included between March 2022 and April 2025, with last follow-up in July 2025.

INTERVENTIONS Patients were randomized to undergo CRT-PHR (n = 720), including assessment of pulse pressure, diastolic arterial pressure, fluid responsiveness, and bedside echocardiography, to tailor fluids, vasopressors, and inotropes, vs usual care (n = 747).

MAIN OUTCOMES AND MEASURES The primary outcome was a hierarchical composite of mortality, duration of vital support (vasoactives, mechanical ventilation, and kidney replacement therapy), and length of hospital stay assessed at 28 days. A win ratio was calculated for the primary outcome by comparing all possible patient pairs, starting with the first event in the hierarchy and stratified by median APACHE (Acute Physiology and Chronic Health Evaluation) II score at admission. Secondary outcomes were mortality, vital support–free days, and length of hospital stay at 28 days.

RESULTS From 1501 randomized patients, 1467 were included in the primary analysis (mean age, 66 [17] years; 43.3% female). There were 131 131 wins (48.9%) in the CRT-PHR group vs 112 787 (42.1%) in the usual care group for the hierarchical composite primary outcome, with a win ratio of 1.16 (95% CI, 1.02-1.33; *P* = .04). Individual wins for death were 19.1% vs 17.8%; duration of vital support, 26.4% vs 21.1%; and length of hospital stay, 3.4% vs 3.2% in the intervention vs usual care groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with early septic shock, a personalized hemodynamic resuscitation protocol targeting capillary refill time was superior to usual care for the primary composite outcome, primarily due to a lower duration of vital support.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05057611

Visual Abstract
Research Summary
Editorial
Supplemental content

Group Information: The ANDROMEDA-SHOCK-2 Investigators appear at the end of the article. Members of the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN) appear in Supplement 3.

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Research in septic shock has been focused on determining the best resuscitation strategy to reduce mortality and improve patient-centered outcomes. Unfortunately, the optimal management of fluids and vasoactive agents remains uncertain.[1] One possible explanation lies in the substantial heterogeneity of patients with septic shock, which may limit the effectiveness of nonpersonalized resuscitation strategies.[2] Indeed, recent trials comparing liberal vs restrictive fluid administration[3] or high vs low mean arterial pressure (MAP) targets[4] have failed to improve patient-centered outcomes. Accordingly, how to personalize hemodynamic resuscitation in septic shock is a research priority raised by experts and recent guidelines.[5-7]

Septic shock resuscitation relies on the assumption that hemodynamic optimization will improve tissue perfusion and revert cell metabolic derangements.[6] Assessment of capillary refill time (CRT) may identify tissue hypoperfusion,[8,9] while its evolution could reflect the progress of resuscitation.[10] In the ANDROMEDA-SHOCK trial, CRT-targeted resuscitation was associated with faster recovery of organ dysfunction, less fluid administration,[11] and higher likelihood of survival[12] compared with lactate-targeted resuscitation.

Diverse pathogenic mechanisms, such as hypovolemia, vasoplegia, and cardiac dysfunction, are involved and overlap in septic shock.[2] Identifying the predominant hemodynamic pattern is challenging, especially when advanced monitoring is not available and initial resuscitative decisions have to be taken immediately after intensive care admission. Analysis of simple clinical physiological signals at the bedside may be helpful. For instance, a low diastolic arterial pressure (DAP) reflects decreased vascular tone, while a narrow pulse pressure may be associated with a low stroke volume.[13,14] However, the impact of integrating personalized hemodynamic interventions with CRT as a resuscitation target during early stages of septic shock has not been previously studied.

Building on this, the ANDROMEDA-SHOCK-2 trial designed and assessed the efficacy of a personalized hemodynamic resuscitation (PHR) protocol incorporating sequential multilayered assessments of diverse physiological signals to tailor fluids, vasopressors, and inotropes, targeting CRT normalization. The study aimed to compare the effect of this strategy vs usual care on a hierarchical composite outcome of mortality, duration of vital support, and length of hospital stay in patients with early septic shock.

Key Points

Question Does a personalized hemodynamic resuscitation strategy targeting capillary refill time normalization improve outcomes in early septic shock compared with usual care?

Findings In this randomized clinical trial including 1467 patients with septic shock treated in 86 intensive care units, a personalized hemodynamic resuscitation strategy had a significant beneficial effect on the composite hierarchical outcome comprising mortality, duration of vital support, and length of stay through 28 days after randomization, compared with usual care (win ratio, 1.16).

Meaning A personalized hemodynamic resuscitation strategy targeting capillary refill time normalization improves patient-centered outcomes in early septic shock.

Methods

Trial Design, Setting, and Oversight

ANDROMEDA-SHOCK-2 was an investigator-generated, multicenter, randomized clinical trial comparing a personalized hemodynamic resuscitation protocol targeting capillary refill time (CRT-PHR) vs usual care in patients with early septic shock. The trial was conducted in 86 intensive care units across 19 countries from the Americas, Europe, and Asia between March 2022 and April 2025, with last follow-up in July 2025. The trial protocol[15] and statistical analysis plan[16] are available in Supplement 1. The trial was overseen by an independent data and safety monitoring board, with 2 interim analyses performed after 200 and 1125 patients were enrolled.[16] The trial was approved by the institutional review board at each participating site. Written informed consent was obtained from patients or their legal authorized representatives according to local regulations. The trial is reported in accordance with the 2025 Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[17]

Patients and Eligibility Criteria

Consecutive adult patients (aged ≥18 years) with septic shock were considered eligible. Septic shock was defined as suspected or confirmed infection, plus hyperlactatemia (≥2.0 mmol/L), and requirement of norepinephrine to maintain a MAP of at least 65 mm Hg after an intravenous fluid load of at least 1000 mL.[18] Patients could be identified within the intensive care unit, emergency department, operating theater, or hospital wards. Patients were recruited up to 4 hours after inclusion criteria were met. Exclusion criteria and full definitions are available in Supplement 1.

Randomization

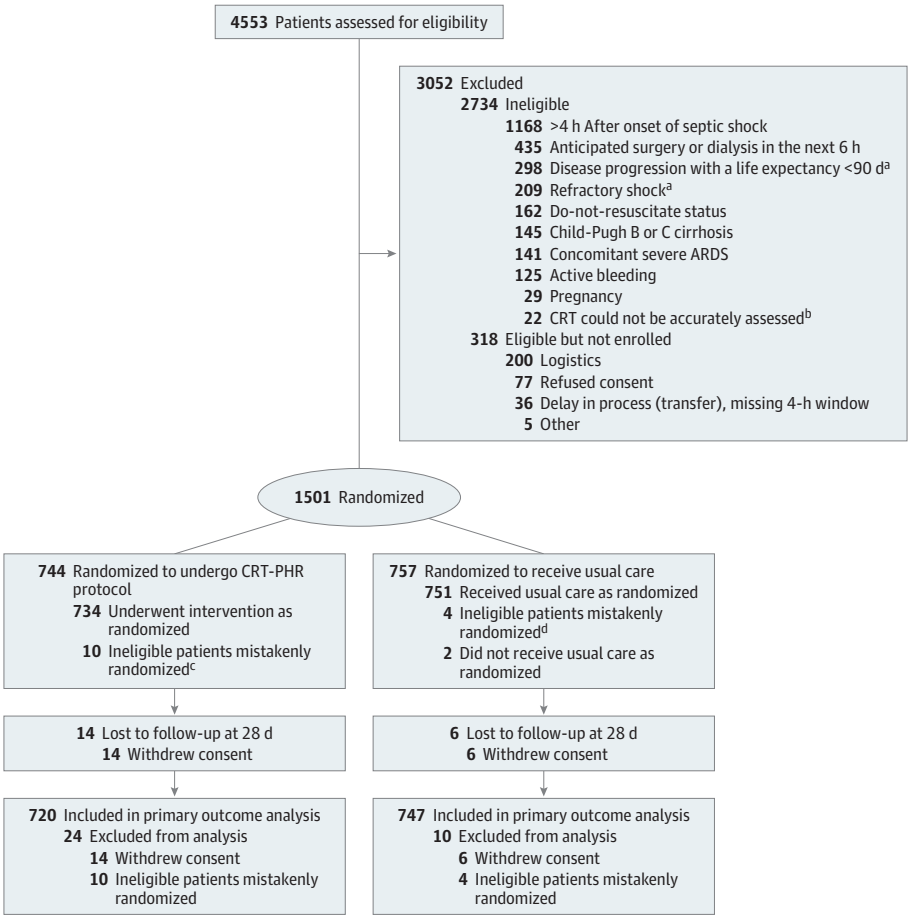
Participants were randomized in a 1:1 ratio to the CRT-PHR or usual care group (**Figure 1**), with stratification by center and using permuted blocks of variable size, using a web-based system (Castor EDC). Allocation concealment was ensured through central randomization. The trial was unblinded to patients and clinicians.

Trial Procedures

The steering committee developed the CRT-PHR algorithm through a consensus process based on physiological and clinical data regarding peripheral perfusion as a resuscitation target,[11] interpretation of macrohemodynamic patterns,[2,19,20] individual response to fluids,[21] and selective use of critical care echocardiography.[22]

The CRT-PHR algorithm was based on 4 fundamental pillars: (1) CRT normalization as the target of hemodynamic resuscitation; (2) baseline identification of individual hemodynamic patterns of cardiovascular dysfunction (persistent hypovolemia, vasoplegia, and cardiac dysfunction) by simple

Figure 1. Flow of Participants in the ANDROMEDA-SHOCK-2 Trial



ARDS indicates acute respiratory distress syndrome; CRT, capillary refill time; CRT-PHR, capillary refill time personalized hemodynamic resuscitation.

[a]Assessed by the treating clinician.

[b]Due to peripheral vascular disease, hypothermia, darker skin tone, or rheumatological diseases, such as Raynaud syndrome.

[c] Reasons included not meeting inclusion criteria (n = 1), liver cirrhosis (n = 2), imminent surgery or acute dialytic procedure within 6-hour period (n = 1), active bleeding at randomization (n = 1), severe ARDS at randomization (n = 1), randomized beyond 4-hour window following septic shock diagnosis (n = 3), and refractory shock at randomization (n = 1).

[d]Reasons included not meeting inclusion criteria (n = 1), liver cirrhosis (n = 1), imminent surgery or acute dialytic procedure within 6-hour period (n = 1), and refractory shock at randomization (n = 1).

clinical tools (pulse pressure and DAP) and basic bedside echocardiography, followed by specific interventions; (3) systematic fluid-responsiveness assessment before any fluid resuscitation; and (4) 2 acute (1-hour) hemodynamic tests: a trial of a higher MAP target and a trial of a fixed low-dose dobutamine.

CRT Assessment

CRT was assessed by applying firm pressure to the ventral surface of the distal phalanx of a finger, using a glass microscope slide. The pressure was increased until the skin was blank, maintained for 10 seconds, and then released. The time required to return to the normal skin color was measured with a chronometer and a refill time longer than 3 seconds was defined as abnormal.

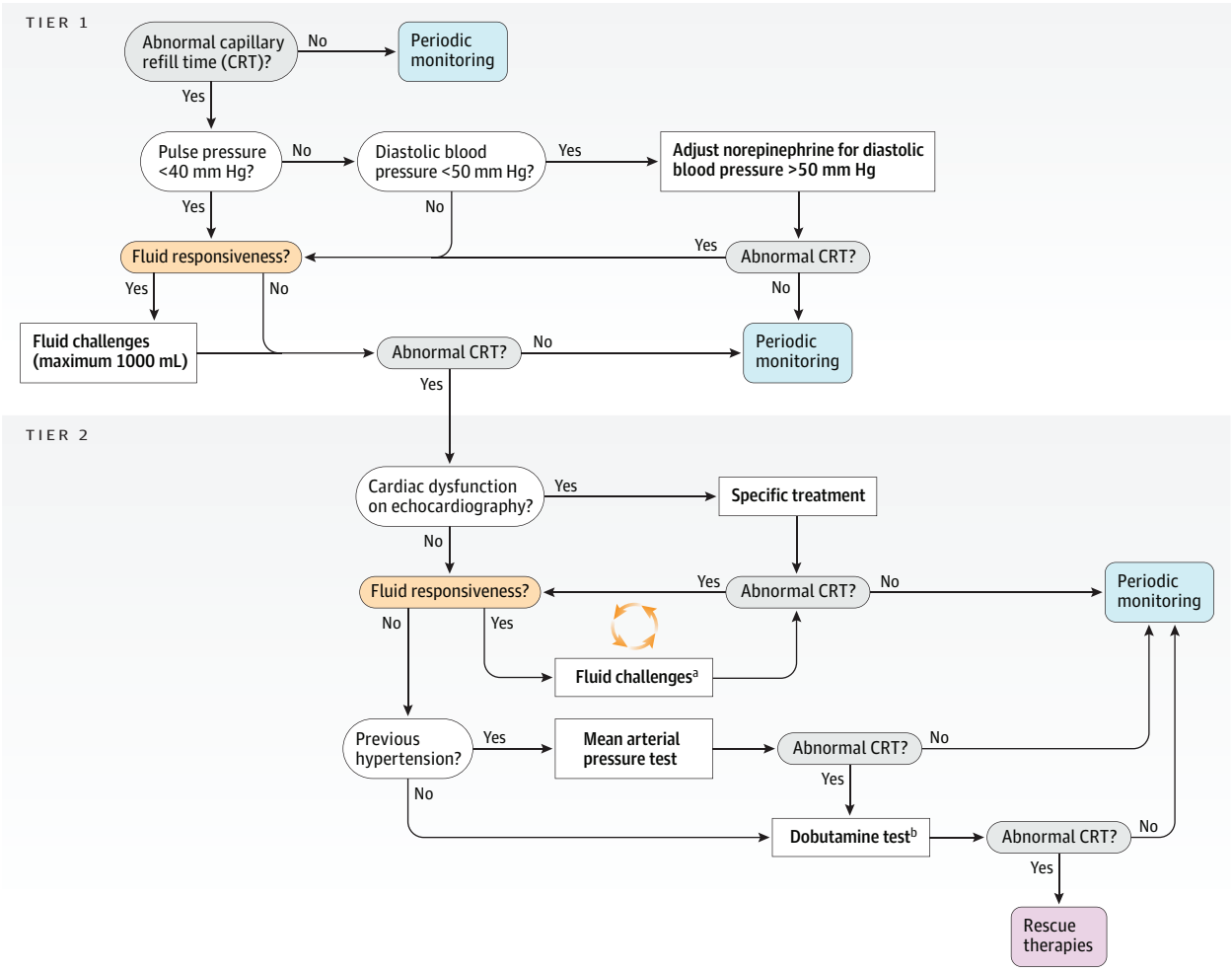
CRT-PHR Overview

Patients randomized to the CRT-PHR group underwent a sequential multilayered personalized resuscitation during a 6-hour study period aimed at normalizing CRT (**Figure 2**). Patients with a normal CRT at baseline did not receive further resuscitative interventions unless CRT became abnormal during subsequent hourly assessments within the 6-hour time frame. Patients with abnormal CRT received CRT-PHR implemented in 2 progressive tiers.

Tier 1 started with the evaluation of pulse pressure. In those patients with a pulse pressure less than 40 mm Hg, fluid responsiveness was assessed, and in those patients identified as fluid responsive, a 500-mL fluid bolus (of crystalloid or colloid) was administered in 30 minutes and CRT reassessed. If still abnormal, a second fluid bolus was administered in fluid-responsive patients. Meanwhile, in those with a pulse pressure of 40 mm Hg or higher and a simultaneous DAP less than 50 mm Hg, norepinephrine was titrated to reach a DAP of 50 mm Hg or higher (DAP adjustment). If these tier 1 interventions failed to normalize CRT, the patient moved to tier 2.

Tier 2 started with basic echocardiography to rule out cardiac dysfunction. In patients with right or left ventricular dysfunction, general treatment recommendations were provided and interventions recorded (right/left ventricular optimization), although no mandatory therapy was part of the CRT-PHR algorithm (Supplement 1). If this intervention failed to normalize CRT or cardiac dysfunction was ruled out, fluid responsiveness was reassessed and further fluid boluses were administered in fluid-responsive patients until normalizing CRT, reaching safety limits, or the patient became unresponsive, whichever came first. If the CRT goal was not achieved, a MAP test was performed only in patients who were chronic hypertensive, by transiently increasing norepinephrine to

Figure 2. Capillary Refill Time Personalized Hemodynamic Resuscitation (CRT-PHR) Algorithm



CRT indicates capillary refill time.

[a]Perform successive fluid challenges until CRT normalizes, fluid responsiveness becomes negative, or safety limits are met.

[b]If patient already received dobutamine due to cardiac dysfunction treatment, skip this step.

attain a MAP of 80 to 85 mm Hg for 1 hour. If the CRT goal was met, this MAP level was maintained throughout the 6-hour study period. Otherwise, norepinephrine was decreased to the previous dose and the patient moved to a dobutamine test with a fixed low dose (5 µg/kg/min) for 1 hour. Dobutamine was maintained only in those with normalized CRT.

In all CRT-PHR stages, normalization of CRT prompted hourly reassessments until protocol completion, without additional resuscitative interventions, while standard goals of care were maintained in accordance with recent guideline recommendations.[12] The clinical team could override the CRT-PHR if deemed in the patient's best interest.

The usual care group was treated according to local protocols and/or international guidelines.[23] Fluid-responsiveness assessment and echocardiography were allowed but not mandated. CRT measurements were only requested at baseline and at 6 hours.

Protocol Training and Adherence

Before recruitment began, all participating clinicians at each site (medical operators) completed mandatory training on trial procedures and protocol implementation. Training included instructional videos and manuals, case-based exercises with fictitious patients, and virtual sessions with the study coordinating center. If a patient was randomized to the CRT-PHR group, trained medical operators executed the protocol. Meanwhile, patients allocated to the usual care group were resuscitated by attending intensivists, who oversaw all care-related decisions. After the 6-hour study period, clinical management of both groups was at the discretion of the attending physicians.

Protocol adherence was audited by a dedicated team from the Fundación Valle del Lili, who identified protocol deviations and nonadherence (protocol violations) by weekly case-by-case analysis of recruited patients in the CRT-PHR group,

according to predefined critical nodes of the algorithm (Supplement 1). In all these cases, participant centers received early feedback from the team.

Outcomes

The primary outcome was a hierarchical composite outcome: (1) all-cause mortality within 28 days, (2) duration of vital support (vasoactives, mechanical ventilation, and kidney replacement therapy) truncated at day 28, and (3) length of hospital stay truncated at day 28. Duration of vital support was defined as the time between randomization and the cessation of all vital support. For patients who resumed vital support, the time of final support cessation was the end of the last period.

Secondary outcomes tested in hierarchical order were (1) all-cause mortality, (2) vital support-free days within 28 days (defined as the number of days between randomization and 28 days after randomization, in which the patient is alive and not requiring cardiovascular, respiratory, and/or kidney support), and (3) length of hospital stay (defined as the number of days between randomization and the day of hospital discharge or death, truncated at day 28). Tertiary outcomes are described at length in Supplement 1. Patients were followed up until day 90 since randomization or death.

Statistical Analysis

For the usual care group, we assumed a 28-day mortality of 39%, mean (SD) number of days needing life support truncated at 28 days among survivors of 5.6 (6.7) and a length of hospital stay truncated at 28 days among survivors of 15.6 (10.1) days, based on the ANDROMEDA-SHOCK trial.[11] We considered that the intervention group would reduce mortality to 33%, shorten mean (SD) days using life support among survivors to 4.3 (6.2), and shorten length of hospital stay among survivors to 14 (9.9) days. Using the win ratio method with these 3 components and with 1500 patients enrolled, the trial had a power of 88% to show superiority in the hierarchical composite outcome for a 2-sided α of .05. Because substantial loss to follow-up was not expected in this setting, no adjustment was made to the sample size for potential attrition.

Analysis of treatment effect considered an intention-to-treat population, defined as all participants who adhered to inclusion and exclusion criteria, were randomized, and consented to participate. The primary outcome was analyzed using the stratified win ratio method, using treatment as a fixed effect, with median Acute Physiology and Chronic Health Evaluation (APACHE) II score as a stratifying variable.[24] The stratified win ratio could be expressed as the proportion of pairwise comparisons for which the intervention won over the control, divided by the proportion of pairwise comparisons for which the control won, considering the hierarchical ordering of the outcomes. We considered death within 28 days as a binary event, and if both patients in a pair died, it was classified as an early tie and no further primary hierarchical outcomes were considered. The bootstrap resampling method was used to calculate the 95% CI for the win ratio and *P* value for the hypothesis test.

Secondary outcomes were analyzed with a gatekeeping procedure to preserve overall type I error at .05. Thus, the assessment of statistical significance of secondary outcomes was performed only if the preceding outcome in the hierarchy met the threshold for statistical significance and is further detailed in the statistical analysis plan (Supplement 1). No adjustment for multiple comparisons was applied for analyses of tertiary outcomes and subgroups. Thus, these results should be interpreted as exploratory. All analyses were performed using R version 4.2.3 software (R Foundation).

Results

Patient Characteristics

We enrolled 1501 patients (eFigure 1 and eTable 1 in Supplement 2). Geographical distribution of recruited patients included the Americas (n = 816), Europe (n = 609), and Asia (n = 76). A total of 744 patients were randomized to the CRT-PHR group and 757 to the usual care group. Twenty patients withdrew consent, while 14 were incorrectly randomized, leaving a final cohort of 1467 patients for the analysis: 720 in the CRT-PHR group and 747 in the usual care group (Figure 1). Patients had similar clinical-demographic characteristics at baseline (**Table 1**) (eTable 2 in Supplement 2).

Protocol Interventions

During the 6-hour study period, a higher percentage of patients normalized CRT in the CRT-PHR group compared with usual care (85.9% vs 61.7%). For those patients who normalized CRT in the CRT-PHR group, this was achieved in 65% and 35% of patients during tiers 1 and 2, respectively. Personalized hemodynamic interventions performed and the number of patients normalizing CRT after each intervention are shown in eFigure 2 and eTable 3 in Supplement 2. In the CRT-PHR group, a total of 262 patients (36.4%) started and remained with a normal CRT throughout the study period, whereby they did not receive further hemodynamic interventions. In the usual care group, 62% of patients had fluid responsiveness assessed at any time point, while 68% had basic echocardiography assessments.

Overall, patients randomized to the CRT-PHR group received less resuscitation fluids (595 mL vs 847 mL; mean difference, −251 mL [95% CI, −316 to −187]), received more dobutamine (84/684 [12.3%] vs 37/694 [5.3%]; difference, 7.0% [95% CI, 4.0%-9.9%]), had lower central venous pressure (9.1 mm Hg vs 9.8 mm Hg; mean difference, −0.6 mm Hg [95% CI, −1.1 to −0.1]), and had lower lactate levels (3.2 mmol/L vs 3.5 mmol/L; mean difference, −0.3 mmol/L [95% CI, −0.5 to −0.1]) by the end of the 6-hour study period compared with usual care (**Table 2**) (eTables 4 and 5 in Supplement 2).

Patients with normal CRT at baseline who were randomized to the CRT-PHR group had less fluid-responsiveness assessments (71/286 [24.8%] vs 155/269 [57.6%]; difference, −32.8% [95% CI, −40.5% to −25.1%]) and received less resuscitation fluids (210 mL vs 441 mL; mean difference, −231 mL [95% CI, −312 to −150]) compared with the usual care group (eTable 6 in Supplement 2). Conversely, among patients with abnormal CRT at baseline randomized to the CRT-PHR group, fluid-responsiveness assessment (390/408 [95.6%] vs

Table 1. Patient Characteristics at Baseline

Characteristic	No./total No. (%)	
	CRT-PHR group (n = 720)	Usual care group (n = 747)
Age, median (IQR), y	66.0 (52.0-74.0)	65.0 (51.0-76.0)
Sex, No. (%)		
Female	302 (41.9)	334 (44.7)
Male	418 (58.1)	413 (55.3)
Weight, median (IQR) [total No.], kg	70.0 (60.0-80.0) [n = 717]	70.0 (60.4-80.0) [n = 747]
Severity scores, median (IQR)		
APACHE II[a]	19.0 (14.0-24.0)	18.0 (13.0-23.0)
SOFA [total No.][b]	8.0 (7.0-11.0) [n = 719]	8.0 (7.0-10.0) [n = 745]
Charlson Comorbidity Index[c]	4.0 (2.0-5.0)	3.0 (2.0-5.0)
Comorbidities		
Chronic hypertension	162/705 (23.0)	179/730 (24.5)
Diabetes	167/706 (23.7)	161/731 (22.0)
Chronic pulmonary disease	81/703 (11.5)	65/730 (8.9)
Diabetes with chronic complications	58/701 (8.3)	47/726 (6.5)
Nonhematological cancer	46/702 (6.6)	30/727 (4.1)
Hematological cancer	12/700 (1.7)	21/726 (2.9)
Source of infection		
Abdominal	350/717 (48.8)	343/745 (46.0)
Respiratory	126/717 (17.6)	156/745 (20.9)
Urinary	151/717 (21.1)	131/745 (17.6)
Cutaneous and soft tissue	42/717 (5.9)	55/745 (7.4)
Bloodstream	27/717 (3.8)	39/745 (5.2)
Bone and joint	5/717 (0.7)	7/745 (0.9)
Central nervous system	6/717 (0.8)	5/745 (0.7)
Mediastinitis	6/717 (0.8)	4/745 (0.5)
Other[d]	4/717 (0.6)	5/745 (0.7)
Microbiologically confirmed infection[e]	454/707 (64.2)	470/741 (63.4)
Time from meeting septic shock criteria to randomization, median (IQR), h	2 (1-3)	2 (1-3)
Organ support at baseline		
Respiratory		
None	82/719 (11.4)	93/741 (12.6)
Low-flow oxygen	221/719 (30.7)	213/741 (28.7)
High-flow nasal cannula	56/719 (7.8)	52/741 (7.0)
Noninvasive mechanical ventilation	23/719 (3.2)	18/741 (2.4)
Invasive mechanical ventilation	337/719 (46.9)	365/741 (49.3)
Cardiovascular		
Norepinephrine	720/720 (100.0)	747/747 (100.0)
Vasopressin	166/701 (23.7)	149/726 (20.5)
Epinephrine	8/700 (1.1)	13/726 (1.8)
Dobutamine	8/701 (1.1)	5/726 (0.7)
Other[f]	1/701 (0.1)	2/726 (0.3)
Hemodynamic- and perfusion-related variables		
Intravenous fluid loading, median (IQR), mL[g]	1500 (1000-2000)	1500 (1000-2000)
Intravenous fluid loading per weight, median (IQR), mL/kg	22.1 (14.3-30.8)	21.4 (14.7-30.4)
Mean arterial pressure, median (IQR), mm Hg	69 (64-76)	69 (65-76)
Heart rate, median (IQR), beats/min	102 (89-116)	105 (89-117)
Norepinephrine dose, median (IQR), µg/kg/min	0.23 (0.12-0.40)	0.21 (0.10-0.39)
Serum lactate, median (IQR), mmol/L	3.7 (2.7-5.5)	3.6 (2.7-5.3)
Serum lactate >4.0 mmol/L, No. (%)	315 (43.8)	314 (42.0)
Capillary refill time, median (IQR) [total No.], s	4.0 (2.4-5.7) [n = 719]	4.0 (3.0-6.0) [n = 742]
Capillary refill time >3 s, No. (%)	419/719 (58.3)	459/742 (61.9)
Venous-to-arterial carbon dioxide difference, median (IQR) [total No.], mm Hg	6.8 (4.4-9.0) [n = 620]	6.3 (4.1-9.0) [n = 616]
Venous-to-arterial carbon dioxide difference >6 mm Hg	324/620 (52.3)	314/628 (51.0)
Central venous oxygen saturation, median (IQR) [total No.], %	74 (67-81) [n = 626]	73 (66-79) [n = 630]
Central venous oxygen saturation <75%	330/626 (52.7)	362/630 (57.5)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRT-PHR, capillary refill time personalized hemodynamic resuscitation; SOFA, Sequential Organ Failure Assessment.

[a] Scores range from 0 to 33, with higher scores indicating a greater burden of disease.

[b] Scores range from 0 to 24, with higher scores indicating 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 rate of 50%).

[c] Scores range from 0 to 71, with higher scores indicating greater severity of illness and risk of in-hospital death (eg, a score of 22 in a patient with sepsis predicts an in-hospital mortality rate of 45%).

[d] Unknown source (n = 6), endocarditis (n = 1), gynecologic (n = 1), and myocarditis (n = 1).

[e] Defined as any positive culture or diagnostic test confirming infection.

[f] Phenylephrine (n = 2), milrinone (n = 1), and methylene blue (n = 1).

[g] Intravenous fluid loading and intravenous fluid loading per weight included fluid received during the interval between presentation to the emergency department and randomization.

327/430 [76.1%]; difference, 19.5% [95% CI, 15.0% to 24.0%]) and inotropes administration (72/399 [18.0%] vs 26/427 [6.1%]; difference, 12.0% [95% CI, 7.6%-16.4%]) were more frequent compared with usual care (eTable 6 in Supplement 2). Evolution of hemodynamics and tissue perfusion variables up to day 3 is shown in eTables 4 and 5 in Supplement 2.

In the CRT-PHR group, protocol deviations and violations were observed in 111 of 720 (15%) and 44 of 720 patients (6%), respectively (eFigure 3 and eTable 7 in Supplement 2). DAP augmentation, MAP tests, and dobutamine tests were not conducted due to preemptive safety considerations in 6, 13, and 19 patients, respectively. One dobutamine test had to be stopped because of hypotension, which was reversed after drug discontinuation.

Table 2. Hemodynamic Therapies and Resuscitation-Related Variables at Hour 6

	CRT-PHR group	Usual care group	Absolute difference (95% CI)
Therapy			
Norepinephrine, No./total No. (%)	648/684 (94.7)	634/694 (91.4)	3.4 (0.7 to 6.1)
Norepinephrine dose, mean (SD), μgr/kg/min	0.28 (0.34) [n = 655]	0.27 (0.41) [n = 634]	−0.01 (−0.05 to 0.03)
Vasopressin, No./total No. (%)	251/684 (36.7)	229/694 (33.0)	3.7 (−1.3 to 8.7)
Dobutamine, No./total No. (%)	84/684 (12.3)	37/694 (5.3)	7.0 (4.0 to 9.9)
Volume of resuscitation fluids, mean (SD), mL	595 (679) [n = 672]	847 (832) [n = 676]	−251 (−316 to −187)
Net fluid balance, mean (SD), mL	990 (1016) [n = 629]	1227 (1225) [n = 622]	−242 (−385 to −99)
Hemodynamic and perfusion-related variable			
Central venous pressure, mean (SD), mm Hg	9.1 (4.1) [n = 541]	9.8 (4.8) [n = 544]	−0.6 (−1.1 to −0.1)
Mean arterial pressure, mean (SD), mm Hg	74.1 (9.4) [n = 682]	73.6 (9.0) [n = 690]	0.6 (−0.5 to 1.7)
Capillary refill time, mean (SD), s	2.8 (1.4) [n = 679]	3.4 (1.9) [n = 684]	−0.6 (−0.7 to −0.4)
Lactate level, mean (SD), mmol/L	3.2 (2.4) [n = 659]	3.5 (3.0) [n = 664]	−0.3 (−0.5 to −0.1)
Central venous oxygen saturation, mean (SD), %	74.4 (8.9) [n = 588]	72.4 (9.9) [n = 596]	1.9 (0.8 to 3.0)

Abbreviation: CRT-PHR, capillary refill time personalized hemodynamic resuscitation.

Table 3. Primary and Secondary Outcomes

Outcome	CRT-PHR group (n = 720)	Usual care group (n = 747)	Effect estimate (95% CI)	*P* value
Primary outcome through 28 d, total No. of wins (%)				
Hierarchical composite of death, duration of vital support, and length of hospital stay[a]	131 131 (48.9)	112 787 (42.1)	SWR, 1.16 (1.02 to 1.33)	.04
Secondary outcomes				
All-cause mortality within 28 d, No. (%)[b]	191 (26.5)	199 (26.6)	HR, 0.99 (0.81 to 1.21)	.91
Vital support-free days within 28 d[c]				
Mean (SD)	16.5 (11.3)	15.4 (11.4)	pOR, 1.28 (1.06 to 1.54)	NA
Median (IQR)	23.0 (0 to 25.0)	22.0 (0 to 25.0)		
Length of hospital stay up to day 28, d[d]				
Mean (SD)	15.3 (9.0)	16.2 (9.4)	MD, −0.85 (−1.80 to 0.10)	NA
Median (IQR)	13.0 (8.0 to 25.0)	15.0 (8.0 to 28.0)		

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRT-PHR, capillary refill time personalized hemodynamic resuscitation; HR, hazard ratio; MD, mean difference; NA, not applicable; pOR, proportional odds ratio; SWR, stratified win ratio.

[a] The stratified win ratio was calculated using treatment as a fixed effect stratified by the median APACHE II score. Patients in the CRT-PHR group were compared with those in the usual care group within each APACHE II stratum, following a hierarchical order of the primary outcome assessed within 28 days: death, duration of vital support, and length of hospital stay. If 1 patient survived and the other did not, the survivor's group was assigned the win. If both patients died, the comparison was considered an early tie. If both survived, the comparison proceeded to duration of vital support and, if tied (same duration in days), to length of hospital stay. The stratified win ratio reflects the number of wins in the CRT-PHR group vs the usual care group, accounting for outcome hierarchy and stratification. Duration of vital support was defined as the time between randomization and cessation of all vital support. For patients who resumed vital support, the time of final support cessation was the end of the last period.

[b] HR was calculated with Cox proportional hazards, with adjustments for baseline APACHE II score.

[c] Vital support–free days were defined as the number of days between the date of randomization and the maximum end date of vasopressor use, mechanical ventilation, or kidney replacement therapy, within the first 28 days. Any death occurring within 28 days was assigned a value of 0 support-free days. The pOR was calculated with cumulative logistic regression adjusted for baseline APACHE II score.

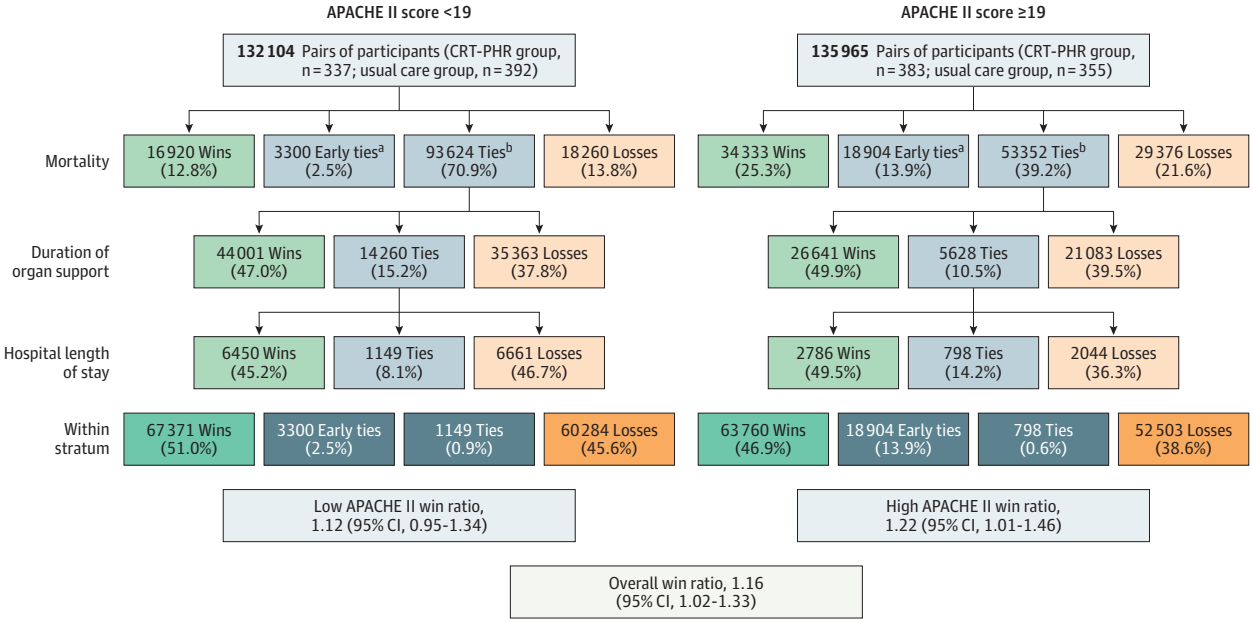
[d] MD was calculated with a generalized linear model with generalized additive model for location, scale and shape, adjusted for baseline APACHE II score.

Outcomes

At 28 days after randomization, we observed 131 131 wins (48.9%) for the CRT-PHR group over 112 787 (42.1%) in the usual care group, yielding a stratified win ratio of 1.16 (95% CI, 1.02-1.33; *P* = .04) (**Table 3** and **Figure 3**). The total number of ties was 24 151 (9.0%). Of the 3 components of the win ratio, duration of vital support yielded the highest number of wins to losses (eTable 8 in Supplement 2); individual wins for death were 19.1% vs 17.8%; duration of vital support, 26.4% vs 21.1%; and length of hospital stay, 3.4% vs 3.2% in the intervention vs usual care groups, respectively.

Among secondary outcomes, there was no significant difference in 28-day mortality between the CRT-PHR and usual care groups (26.5% vs 26.6%; hazard ratio, 0.99 [95% CI,

Figure 3. Primary Outcome Analysis



Distribution of wins, ties, and losses for the CRT-PHR group among both APACHE II strata at each level of the hierarchical primary composite outcome. Every possible pair of participants between groups was compared in a hierarchical fashion with a win, loss, or tie determined by the outcome evaluated at each level of the hierarchy. Percentages are calculated for each level of the hierarchy.

APACHE indicates Acute Physiology and Chronic Health Evaluation; CRT-PHR, capillary refill time personalized hemodynamic resuscitation.

[a]Early ties were determined when both participants in the pair died before 28 days following randomization. No further pairwise outcome comparisons were made for early ties.

[b]Ties were determined when both participants survived 28 days or more following randomization.

0.81-1.21]; P = .91). Patients in the CRT-PHR group had a higher number of mean (SD) organ support–free days within 28 days (16.5 [11.3] vs 15.4 [11.4]; proportional odds ratio, 1.28 [95% CI, 1.06-1.54]) and faster decrease in SOFA (Sequential Organ Failure Assessment) score within 7 days compared with the usual care group (eTables 9 and 10 in Supplement 2). Tertiary outcomes are presented in eTable 11 in Supplement 2. Vital support requirements throughout the study period are shown in eTable 12 in Supplement 2. There was no effect modification for the subgroups assessed (eFigure 4 and eTables 13 and 14 in Supplement 2). Use of adjunctive therapies and antimicrobial and surgical source control is shown in eTables 15 and 16 in Supplement 2. A post hoc analysis of treatment effect by participating centers is shown in eFigure 5 in Supplement 2. Five 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.

Discussion

In this trial including patients with early septic shock, a CRT-PHR strategy was superior to usual care on a hierarchical composite outcome of mortality, duration of vital support, and length of hospital stay at day 28. These results were mainly driven by a shorter duration of vital support.

The development of personalized hemodynamic resuscitative strategies is considered a top priority on the septic shock research agenda.[5,6] However, there has been limited progress in this direction, explained partly by the extreme complexity of designing and conducting trials in which the intervention process is probably a research objective by itself. When comparing a personalized resuscitation strategy with usual care, there are additional challenges, such as training, monitoring, and data analysis, particularly to assess gradients of interventions between groups. The present trial used a comprehensive approach to address these challenges, opening new perspectives for future studies.

The ANDROMEDA-SHOCK trial established CRT as a valid target for hemodynamic resuscitation in septic shock[11,25,26] by using a standardized sequential algorithm, including fluid responsiveness assessment, and MAP and/or dobutamine tests to achieve perfusion goals.[21] Although the ANDROMEDA-SHOCK-2 trial might appear to have certain similarities at first glance, the novel CRT-PHR protocol introduced key refinements aimed at personalizing resuscitation.[27] This protocol incorporated simple bedside hemodynamic tools, such as pulse pressure, DAP, and basic echocardiography assessments, to identify distinct hemodynamic patterns and tailor resuscitative interventions.[28] The CRT-PHR algorithm had a hierarchical structure of increasing complexity, reserving more labor-intensive assessments (eg, echocardiography)

for patients with persistent CRT abnormalities after simpler tier 1 interventions. Indeed, only 35% of patients transitioned to tier 2. Additionally, the ANDROMEDA-SHOCK-2 algorithm was operationalized around key actionable nodes that were trainable and auditable by data quality monitoring to further enhance its effectiveness and facilitate transition to clinical practice.

The effectiveness of the CRT-PHR algorithm cannot be attributed to a single intervention (ie, administered resuscitation fluids) but to the dynamic interaction between the individual components, which converged into a higher rate of CRT normalization. Patients in the CRT-PHR group with normal baseline CRT underwent fewer tests and received less fluids and inotropes, suggesting a more efficient resuscitation. Moreover, normalization of CRT after hemodynamic interventions may signal effective tissue reperfusion, allowing clinicians to stop resuscitation.[10] Taken together, this may decrease the odds of overresuscitation, organ dysfunction, and organ support requirements, a relevant patient-centered outcome.[26] Indeed, the results of ANDROMEDA-SHOCK-2 support these findings (Table 2).

An important element of acute hemodynamic tests is that they are reversible, which can be continued or not according to response, representing real-time personalization of hemodynamic interventions.[29] Both the MAP and dobutamine tests presented success rates (CRT normalization) of approximately 50%. Additionally, a novel DAP adjustment was integrated, with the aim of eventually improving coronary perfusion and consequently systemic blood flow to restore abnormal CRT.[19,20] Even though CRT normalization rates were lower than with the aforementioned tests, overall CRT values decreased considerably even in patients who did not normalize (eTable 3 in Supplement 2). Further research should explore this in more detail.

To comprehensively assess treatment efficacy in critical care trials, composite end points have been increasingly used.[30-32] These measures are particularly valuable because binary outcomes, such as mortality, often fail to capture the full spectrum of morbidity, including prolonged organ dysfunction and the need for sustained vital support among survivors. Indeed, the latter is relevant because it directly influences patients' recovery trajectories, prolongs the emotional burden for families, and carries major implications for health care system capacity and resource allocation. Thus, composite end points provide a granular and useful view of clinical progression, reflecting both patient-centered outcomes and health care resource utilization.[33-38] The use of the win ratio method as primary outcome analysis in ANDROMEDA-SHOCK-2 had the advantage to assess treatment effect on a composite outcome, but with hierarchical prioritization.[24] In fact, higher weights are placed on outcomes at the top of the hierarchy. Thus, it increased statistical power compared with assessing mortality alone.

Strengths of this study include its generalizability because it was conducted in a diverse range of hospitals across high- and middle-income countries, enhancing external validity. The protocol proved feasible, evidenced by high adherence rates and a low frequency of protocol violations (nonadherence).

Limitations

This study has limitations. First, it was unblinded. However, multiple independent signals favored the CRT-PHR group, highlighting consistency of the observed effects. Second, decisions regarding discontinuation of vasopressors, extubation, and initiation of kidney replacement therapy were made by attending intensivists according to local practice and were not adjudicated. Nonetheless, while variability in clinical decision-making may increase random error, there is no reason to anticipate systematic differences between study groups. Third, the protocol relied on specific measurements, such as CRT testing, that may have been affected by interrater variability; however, this can be mitigated with proper training and standardization. Fluid responsiveness assessment could be challenging in specific scenarios. The study proposed dichotomic thresholds for pulse pressure and DAP that, although physiologically sound, lack prospective clinical validation. Fourth, the protocol may be perceived as labor intensive and impractical in certain clinical contexts. Nonetheless, most patients achieved CRT normalization with tier 1 interventions, and the protocol proved feasible across a broad range of organizational cultures. Fifth, the possibility that more frequent patient assessments in the CRT-PHR group contributed to the observed effect cannot be excluded. However, the reduction in fluid administration, greater use of vasopressors and inotropes at 6 hours, and higher rates of CRT normalization in the CRT-PHR group all point to protocol-specific mechanistic effects as the primary drivers of benefit. Sixth, one could argue that the usual care group may have been unintentionally undertreated. However, this group underwent substantial fluid responsiveness and echocardiographic assessments, received larger volumes of fluids and a similar proportion of adjuvant therapies, and achieved a lower-than-anticipated 28-day mortality, all of which suggest that undertreatment was unlikely. Seventh, even though the low mortality rate observed in both groups could raise concerns about limited power for the primary outcome analysis, the use of the win ratio approach mitigates this risk. Lower mortality rate in both groups decreases the number of ties and, in turn, increases the number of comparisons based on subsequent hierarchical outcomes. Eighth, mandatory training may have led to inadvertent contamination of the usual care group. However, if that was the case, the results may have underestimated the treatment effect. Ninth, variability in standard care practices across centers and countries may have influenced outcomes; however, such heterogeneity reflects real-world conditions and enhances external validity of the results.

Conclusions

Among patients with early septic shock, a personalized hemodynamic resuscitation protocol targeting CRT was superior to usual care for the primary composite outcome of mortality, duration of vital support, and length of hospital stay at day 28, primarily due to a shorter duration of organ support.

ARTICLE INFORMATION

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