The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2022 VOL. 386 NO. 26

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

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ABSTRACT

BACKGROUND

Intravenous fluids are recommended for the treatment of patients who are in septic shock, but higher fluid volumes have been associated with harm in patients who are in the intensive care unit (ICU).

METHODS

In this international, randomized trial, we assigned patients with septic shock in the ICU who had received at least 1 liter of intravenous fluid to receive restricted intravenous fluid or standard intravenous fluid therapy; patients were included if the onset of shock had been within 12 hours before screening. The primary outcome was death from any cause within 90 days after randomization.

RESULTS

We enrolled 1554 patients; 770 were assigned to the restrictive-fluid group and 784 to the standard-fluid group. Primary outcome data were available for 1545 patients (99.4%). In the ICU, the restrictive-fluid group received a median of 1798 ml of intravenous fluid (interquartile range, 500 to 4366); the standard-fluid group received a median of 3811 ml (interquartile range, 1861 to 6762). At 90 days, death had occurred in 323 of 764 patients (42.3%) in the restrictive-fluid group, as compared with 329 of 781 patients (42.1%) in the standard-fluid group (adjusted absolute difference, 0.1 percentage points; 95% confidence interval [CI], −4.7 to 4.9; P=0.96). In the ICU, serious adverse events occurred at least once in 221 of 751 patients (29.4%) in the restrictive-fluid group and in 238 of 772 patients (30.8%) in the standard-fluid group (adjusted absolute difference, −1.7 percentage points; 99% CI, −7.7 to 4.3). At 90 days after randomization, the numbers of days alive without life support and days alive and out of the hospital were similar in the two groups.

CONCLUSIONS

Among adult patients with septic shock in the ICU, intravenous fluid restriction did not result in fewer deaths at 90 days than standard intravenous fluid therapy. (Funded by the Novo Nordisk Foundation and others; CLASSIC ClinicalTrials.gov number, NCT03668236.)

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*A complete list of investigators in the Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 17, 2022, at NEJM.org.

N Engl J Med 2022;386:2459-70.
DOI: 10.1056/NEJMoa2202707

A Quick Take is available at NEJM.org

Septic shock is a leading cause of death worldwide, and improvements in care are warranted.[1,2] Intravenous fluids are administered to improve circulation in these patients, and the Surviving Sepsis Campaign guidelines suggest an initial fixed volume of 30 ml per kilogram of body weight, although the level of certainty for this evidence is low.[1] Owing to insufficient evidence, no recommendation is currently given with regard to the use of restrictive or liberal fluid strategies in patients who still have signs of hypoperfusion after initial resuscitation measures have been taken.[1]

The use of higher volumes of intravenous fluid has been associated with harm in observational studies[3-6] and in randomized trials involving patients with sepsis and septic shock.[7-11] The adverse effects in these patients include worsening of kidney injury,[7] respiratory failure,[8-10] and higher risk of death.[11] However, a recent systematic review of meta-analyses of randomized trials that assessed lower intravenous fluid volumes as compared with higher intravenous fluid volumes in adults with sepsis showed that the quantity and quality of evidence were very low.[12] We conducted the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial to evaluate the effects of restriction of intravenous fluids on mortality and other important outcomes in adult patients with septic shock in the intensive care unit (ICU).

METHODS

TRIAL DESIGN AND OVERSIGHT

CLASSIC is an international, stratified, parallel-group, open-label, randomized clinical trial. Patients underwent screening and randomization between November 27, 2018, and November 16, 2021, in 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, the Czech Republic, the United Kingdom, and Belgium after formal approval was granted at each site. We obtained written informed consent from patients or their legal surrogates according to national regulations. At most sites, enrollment was allowed as an emergency procedure (e.g., with consent from a doctor who was independent of the trial, followed by consent to continue participation obtained at a later time from the patient and the patient's relatives). If consent for participation was withdrawn, the trial intervention was discontinued, and we asked for consent to continue the data collection and inclusion of the patient's data in the analyses.

The trial was funded by the Novo Nordisk Foundation, which had no role in the design or conduct of the trial or the analyses or reporting of the results. The trial protocol, which includes the statistical analysis plan, has been published previously[13] and is available with the full text of this article at NEJM.org. Trial conduct and patient safety were overseen by the Collaboration for Research in Intensive Care in Copenhagen and an independent data and safety monitoring committee. Protocol adherence was assessed at interim analyses conducted when 10% and 30% of the total enrolled population (155 and 466 patients) had been followed for 30 days. Safety was also assessed when 777 patients (50% of the total enrolled population) had been followed for 90 days. Trial data were monitored at the sites by external monitors according to the Good Clinical Practice guidelines of the International Council for Harmonisation and monitored centrally by staff at the coordinating center. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The management committee (listed in the protocol) designed the trial, wrote earlier drafts of the manuscript, and made the decision to submit the manuscript for publication.

TRIAL PATIENTS

We screened patients 18 years of age or older who were in the ICU and had septic shock,[14] which was defined as suspected or confirmed infection, a plasma lactate level of 2 mmol per liter (18 mg per deciliter) or higher, receipt of ongoing infusion of a vasopressor or inotropic agent, and receipt of at least 1 liter of intravenous fluids in the 24 hours before screening.[13] Patients were included if the onset of shock had been within 12 hours before screening. Trial sites were encouraged to systematically screen all patients who met the inclusion criteria. Exclusion criteria are shown in Figure 1 and described along with inclusion criteria and full definitions in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

We performed randomization using a centralized, computer-generated allocation sequence

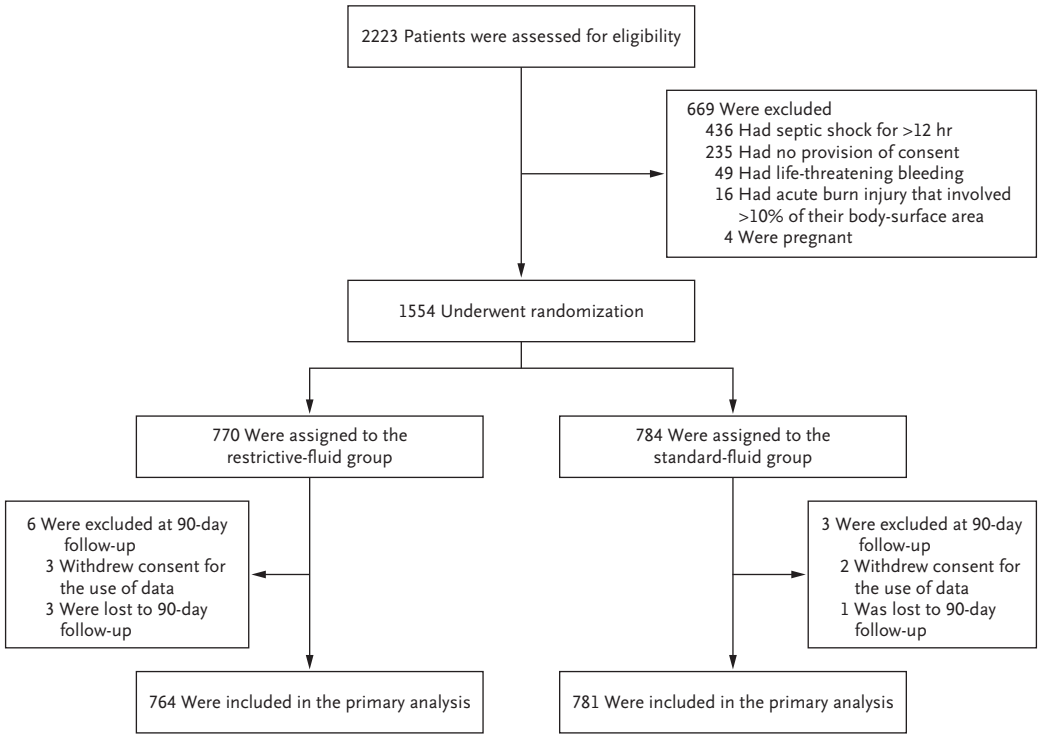


Figure 1. Assessment, Randomization, and Follow-up.

We screened patients 18 years of age or older who were being treated in the intensive care unit for septic shock, which was defined as suspected or confirmed infection, a plasma lactate level of 2 mmol per liter (18 mg per deciliter) or higher, receipt of ongoing circulatory support, and receipt of at least 1 liter of intravenous fluids in the 24 hours before screening. A total of 65 patients met two or more exclusion criteria, and 5 patients were excluded after they had undergone randomization owing to lack of consent to the use of data.

that was stratified according to trial site and the presence or absence of metastatic or hematologic cancer. Eligible patients were randomly assigned in a 1:1 ratio, in permuted blocks of 6 or 8, to receive restrictive intravenous fluid therapy or standard intravenous fluid therapy. Treatment-group assignments were not masked for patients, clinicians, or investigators but were concealed from the data and safety monitoring committee and trial statisticians and from the members of the management committee when they were drafting the first version of the abstract (available in the Supplementary Appendix).

INTERVENTIONS

Enrolled patients were treated with restrictive intravenous fluid therapy or standard intravenous fluid therapy during their stay in the ICU.[7,13] In the restrictive-fluid group, intravenous fluid could only be given under any of the following four conditions. First, intravenous fluids could be given if the patient had severe hypoperfusion, which was defined as a plasma lactate value of at least 4 mmol per liter (36 mg per deciliter) as measured on clinical grounds, a mean arterial pressure below 50 mm Hg despite infusion of a vasopressor or an inotropic agent, mottling beyond the edge of the kneecap (mottling score >2 on a scale of 0 to 5, with higher scores indicating a greater area of mottling)[15], or a urinary output of less than 0.1 ml per kilogram of body weight per hour during the first 2 hours after randomization; if any of these criteria were fulfilled, an intravenous fluid bolus of 250 to 500 ml of isotonic crystalloid (saline or buffered solutions) could be given. Second, the patient could be given intravenous fluids to replace documented fluid losses (e.g., gastrointestinal or drain losses). Third, the patient could be given intravenous fluids to correct dehydration

or electrolyte deficiency because the enteral route was contraindicated. Or fourth, the patient could be given intravenous fluids to ensure a total daily fluid intake of 1 liter, including fluids with medication and nutrition because the enteral route was contraindicated.

No upper limit was set for the amount of intravenous fluids that patients in the standard-fluid group should receive. Intravenous fluid could be administered under any of the following three conditions. First, intravenous fluid should be given as long as the patient had improvement in hemodynamic factors, as described in the 2016 Surviving Sepsis Campaign guidelines.[16] Second, the patient should be given fluids to replace expected or observed losses or to correct dehydration or electrolyte derangements. Or third, the patient should be given maintenance fluid if the ICU had a protocol that recommended it. Enteral and oral fluids, nutrition (enteral or parenteral), and fluid used as a medium for the administration of medication were allowed in both groups. The protocol included recommendations with regard to the types of fluids to be administered to patients in both intervention groups (i.e., isotonic crystalloids for circulatory impairment and losses and albumin only if large amounts of ascites were removed by means of paracentesis) and concomitant interventions for septic shock (i.e., relevant antibiotic agents and source control, norepinephrine as a vasopressor, and renal replacement therapy administered on the basis of conservative criteria[17]). Details about trial interventions and outcomes are provided in the Supplementary Appendix.

The patients received the assigned intervention from the time of randomization until they were discharged from the ICU, for a maximum of 90 days. If a patient was readmitted within 90 days to an ICU participating in the trial, the assigned intravenous fluid intervention was resumed. All other interventions, including the use of diuretics, were at the discretion of the clinicians.

OUTCOME MEASURES

The primary outcome was death within 90 days after randomization. Secondary outcomes were the number of patients who had one or more serious adverse events in the ICU (cerebral, cardiac, intestinal, or limb ischemic events) or had a new episode of severe acute kidney injury, as defined by a modified Kidney Disease: Improving Global Outcomes (KDIGO) stage of 3 on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury, and the use of a modified classification because urinary output data might not have been available from all patients[18]; the number of patients with one or more serious adverse reactions to intravenous crystalloids in the ICU; the number of days alive without life support (i.e., circulatory support, invasive mechanical ventilation, or renal replacement therapy) at day 90; and the number of days alive and out of the hospital at day 90. Data on the outcome measures were obtained from patient medical records by the trial investigators or their delegates. Data from patient medical records or administrative registries were used to determine 90-day mortality, and patients or relatives were contacted for information if needed. We also calculated a Simplified Mortality Score for the Intensive Care Unit on the basis of age, coexisting conditions, and markers of acute disease in the 24-hour period before randomization; scores on this scale range from 0 to 42, with higher scores indicating higher predicted 90-day mortality.[25]

STATISTICAL ANALYSIS

We estimated that 1554 patients would be required for the trial to have 80% power to show an absolute between-group difference of 7 percentage points in 90-day mortality, corresponding to a 15% relative risk reduction or increase at a two-sided alpha level of 0.05, assuming a baseline 90-day mortality of 45%.[7,8,13,19-22]

The statistical analyses were performed according to the published statistical analysis plan, with some modifications, by three of the coauthors, who were unaware of the group assignments.[13] We conducted the primary analyses in the intention-to-treat population, defined as all the patients who had undergone randomization, with the exception of five patients who had been excluded after randomization because they did not consent to the use of any data. We excluded patients in the per-protocol population for whom there were one or more major protocol violations. Additional information is provided in the Supplementary Appendix.

In the primary analyses, we compared data from the two groups using binary logistic regression

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)
Median age (IQR) — yr	71 (62–77)	70 (60–77)
Male sex — no. (%)	452 (59.9)	452 (58.2)
Coexisting condition — no. (%)		
Hematologic or metastatic cancer	128 (17.0)	140 (18.0)
Ischemic heart disease or heart failure	116 (15.4)	151 (19.5)
Chronic hypertension	346 (45.8)	360 (46.4)
Long-term dialysis†	9 (1.2)	12 (1.5)
Median time from ICU admission to randomization (IQR) — hr	3 (1–7)	3 (1–8)
Median predicted 90-day mortality (IQR) — %‡	40 (34–50)	40 (31–50)
Source of ICU admission — no. (%)		
Emergency department or prehospital	297 (39.3)	299 (38.5)
Hospital ward	258 (34.2)	300 (38.7)
Operating or recovery room	173 (22.9)	153 (19.7)
Another ICU	27 (3.6)	24 (3.1)
Focus of infection — no. (%)§		
Gastrointestinal	278 (36.8)	297 (38.3)
Pulmonary	209 (27.7)	206 (26.5)
Urinary tract	119 (15.8)	133 (17.1)
Skin or soft tissue	62 (8.2)	64 (8.2)
Other	85 (11.3)	76 (9.8)
Body weight, blood values, and interventions		
Median body weight (IQR) — kg	77 (67–90)	78 (67–91)
Median highest plasma lactate (IQR) — mmol per liter¶	3.8 (2.7–6.0)	3.9 (2.8–6.1)
Median highest dose of norepinephrine (IQR) — μg/kg/min‖	0.25 (0.12–0.44)	0.23 (0.12–0.41)
Median volume of intravenous fluid 24 hr before randomization (IQR) — ml**	3200 (2000–4700)	3000 (2000–4842)
Use of systemic glucocorticoid — no. (%)	216 (28.6)	226 (29.1)
Median highest plasma creatinine (IQR) — mg/dl††	1.6 (1.1–2.4)	1.6 (1.1–2.5)
Use of respiratory support — no. (%)‡‡	397 (52.6)	377 (48.6)

* All baseline values were missing for 15 patients in the restrictive-fluid group and 8 patients in the standard-fluid group. To convert the values for creatinine to μmol per liter, multiply by 88.4. ICU denotes intensive care unit, and IQR interquartile range.

† Long-term dialysis was defined as the use of hemodialysis (or hemofiltration) or peritoneal dialysis at least once a week before hospital admission.

‡ The predicted 90-day mortality was calculated from the Simplified Mortality Score for the Intensive Care Unit,[25] with scores ranging from 0 to 42 points and corresponding predicted 90-day mortality of 3.3 to 91.0%. Details about the score are provided in the Supplementary Appendix.

§ The listed location was the documented or suspected focus of infection at the time of randomization.

¶ Shown are the highest plasma lactate levels within the 3 hours before randomization; values are equivalent to 32 mg per deciliter in the restrictive-fluid group and 35 mg per deciliter in the standard-fluid group.

‖ The infusion rate of norepinephrine reflects the highest rate within the 3 hours before randomization.

** Volumes of intravenous fluid within the 24 hours before randomization were defined as all crystalloid fluids (any saline, sodium bicarbonate, Ringer's, or Plasma-Lyte solution), colloid fluids (albumin 4, 5, or 20%; or gelatin, hydroxyethyl starch, or dextran solutions), and blood products (units of red cells, plasma, or platelets) the patient had received within the 24 hours before undergoing randomization, independent of location (in-hospital or prehospital) and including intravenous fluids that contained medication or nutrition.

†† Values reflect the highest plasma creatinine level within the 24 hours before randomization.

‡‡ Respiratory support includes the continuous use of invasive or noninvasive mechanical ventilation or continuous positive airway pressure at baseline.

Table 2. Cumulative Fluid Volumes and Balances in ICU in the Two Intervention Groups.*

Variable	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)	Difference (Restrictive vs. Standard)
		milliliters	
Intravenous fluid volume†			
After 1 day‡			
Median (IQR)	500 (0 to 1400)	1,313 (500 to 2500)	−813
Mean	1,024	1,724	−700
After 5 days			
Median (IQR)	1,450 (445 to 3200)	3,077 (1535 to 5300)	−1627
Mean	2,327	3,836	−1509
After 90 days			
Median (IQR)	1,798 (500 to 4366)	3,811 (1861 to 6762)	−2013
Mean	3,414	5,275	−1861
Total fluid volume§			
After 1 day‡			
Median (IQR)	1,843 (964 to 3150)	2,708 (1403 to 4267)	−865
Mean	2,315	3,070	−755
After 5 days			
Median (IQR)	8,864 (4865 to 13,488)	10,800 (6178 to 15,459)	−1936
Mean	9,630	11,181	−1551
After 90 days			
Median (IQR)	10,433 (5024 to 25,567)	12,747 (6453 to 28,110)	−2314
Mean	20,307	23,420	−3113
Cumulative fluid balance¶			
After 1 day‡			
Median (IQR)	725 (0 to 1837)	1,342 (308 to 2759)	−617
Mean	1,100	1,689	−589
After 5 days			
Median (IQR)	1,676 (−137 to 4117)	2,420 (759 to 4996)	−744
Mean	2,297	3,187	−890
After 90 days			
Median (IQR)	1,645 (−461 to 4423)	2,368 (368 to 5517)	−723
Mean	2,302	3,117	−815

* All fluid data were missing for 15 patients in the restrictive-fluid group and 8 patients in the standard-fluid group. The trial protocol was discontinued in 80 patients in the restrictive-fluid group and 51 in the standard-fluid group (Table S2); the trial intervention was discontinued at the request of the patient or surrogate in 50 patients in the restrictive-fluid group and 31 in the standard-fluid group. Data collection was stopped on the day of withdrawal unless permission was granted to continue collection; 27 patients in the restrictive-fluid group and 13 in the standard-fluid group consented to continued data collection.

† Amounts are cumulative volumes of intravenous fluids administered in the ICU (not including blood products and intravenous fluids with medication and nutrition); details on fluids administered and fluid output are shown in Table S3.

‡ Day 1 was from the time of randomization to the next start of the 24-hour fluid chart used by the ICU and lasted a median of 13 hours (interquartile range, 7 to 18).

§ Amounts represent the total volumes of fluid given, including intravenous fluids, blood products, nutrition, intravenous and oral medications, and oral fluid intake.

¶ Amounts represent the total volume of fluid minus the total fluid output, including urinary output, fluid removed by renal replacement therapy, and other fluid output (e.g., bleeding, ascites, diarrhea, or drain losses).

Table 3. Primary and Secondary Outcomes.

Outcome	Restrictive-Fluid Group	Standard-Fluid Group	Adjusted Absolute Difference	Adjusted Relative Risk	P Value
			percentage points		
Primary outcome*					
Death by day 90 — no./total no. (%)†	323/764 (42.3)	329/781 (42.1)	0.1 (95% CI, –4.7 to 4.9)	1.00 (95% CI, 0.89 to 1.13)	0.96
Secondary outcomes‡					
Serious adverse events — no./total no. (%)§	221/751 (29.4)	238/772 (30.8)	–1.7 (99% CI, –7.7 to 4.3)	0.95 (99% CI, 0.77 to 1.15)	0.46
Cerebral ischemia	17/755 (2.3)	18/776 (2.3)			
Myocardial ischemia	16/755 (2.1)	6/776 (0.8)			
Intestinal ischemia	41/755 (5.4)	44/776 (5.7)			
Limb ischemia	18/755 (2.4)	18/776 (2.3)			
Severe acute kidney injury	173/750 (23.1)	189/772 (24.5)			
Serious adverse reaction — no./total no. (%)¶	31/755 (4.1)	32/776 (4.1)	–0.1 (99% CI, –2.8 to 2.6)	0.99 (99% CI, 0.50 to 1.93)	0.95
No. of days alive without life support‖					
Median (IQR)	77 (1 to 87)	77 (1 to 87)	0 (–11 to 11)	—	0.84
Mean	50	51			
No. of days alive and out of the hospital**					
Median (IQR)	21 (0 to 69)	33 (0 to 70)	–12 (–30 to 6)	—	0.84
Mean	33	35			

* Primary outcome data were missing from six patients in the restrictive-fluid group and three in the standard-fluid group.

† Logistic-regression analyses were adjusted according to the stratification variables (site and hematologic or metastatic cancer). The results of the sensitivity analyses of the primary outcome are presented in Table S5.

‡ All secondary outcome data were missing for 23 patients (15 patients in the restrictive-fluid group and 8 in the standard-fluid group). Data were missing on some trial days for an additional 18 patients (who were included in the analyses) because the patient or the patient's surrogate did not consent to continued data collection.

§ In the analysis of serious adverse events in the ICU, 5 patients (in addition to the 23 patients mentioned above) had missing data for severe acute kidney injury. One of the five patients had another serious adverse event; thus only 4 patients had missing data in the composite outcome. Severe acute kidney injury was defined as stage 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO) scale[18] in patients who did not have kidney injury of this stage at the time they underwent randomization.

¶ Shown are numbers of serious adverse reactions to intravenous crystalloid fluids (i.e., generalized tonic–clonic seizures, anaphylactic reactions, central pontine myelinolysis, severe hypernatremia, severe hyperchloremic acidosis, or severe metabolic alkalosis). Full definitions of serious adverse reactions are available in the Supplementary Appendix, and data on individual serious adverse reactions are shown in Table S6.

‖ Shown are the number of days alive without use of invasive mechanical ventilation, circulatory support, or any form of renal replacement therapy within the 90-day follow-up period, as calculated with the use of the van Elteren test after adjustment for site (Table S6).

** The number of days alive and out of the hospital included any readmissions during the 90-day follow-up period and were calculated with the use of the van Elteren test after adjustment for site.

analysis adjusted for the stratification variables (trial site and the presence or absence of hematologic or metastatic cancer) in the intention-to-treat population.[23] Relative risks with 95% confidence intervals were computed with the use of G-computation on the basis of the logistic regression (i.e., the generalized linear models with log and identity links did not converge).[24] We also compared the primary outcome adjusted for stratification variables, the Simplified Mortality Score for the Intensive Care Unit, focus of infection (other foci vs. urinary tract infection),[26] and use of systemic glucocorticoids.[27] We further compared the primary outcome in the per-protocol population and in prespecified subgroups that were defined at baseline according to the use of respiratory support, the presence of acute kidney injury, a plasma lactate level of 4 mmol

per liter or higher, patient body weight of 76 kg or higher, and whether there had been administration of intravenous fluids in an amount of 30 ml or more per kilogram of body weight in the 24 hours preceding randomization.[13]

In the secondary analyses, we compared all dichotomous outcomes in logistic regression analyses of the intention-to-treat population that were adjusted for the stratification variables.[13] We also performed unadjusted Fisher's exact test for the binary outcome measures. We analyzed days alive without life support at 90 days and days alive and out of the hospital at 90 days using the van Elteren test (adjusted for site only), since the assumptions for Poisson or negative binomial distributions were not met.[28] No imputations for missing data were performed, since the percentage of missing data was less than 5% for all outcomes.[13] Statistical significance was indicated by a two-sided P value of less than 0.05 for the primary outcome with corresponding 95% confidence intervals; a P value of less than 0.01 was considered to indicate statistical significance for the subgroup analyses and for the secondary outcomes, with corresponding 99% confidence intervals because of multiple testing.[13,29] We performed all analyses using SAS Enterprise Guide, version 7.1 (SAS Institute), and R software, version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

TRIAL POPULATION

We obtained 90-day vital status for 1545 of the 1554 patients (99.4%): a total of 764 patients in the restrictive-fluid group and 781 in the standard-fluid group (Fig. 1). Patient characteristics at baseline were generally well balanced between the two groups (Table 1 and Table S1 in the Supplementary Appendix). The trial patients were representative of patients in the participating ICUs, except that fewer trial patients may have had pulmonary infections.

During the 90-day trial period, patients in both intervention groups remained in the ICU for a median of 5 days after randomization (interquartile range, 3 to 9 days in the restrictive-fluid group and 3 to 10 days in the standard-fluid group); the intravenous fluid protocols were discontinued in the ICU for 80 of 770 patients (10.4%) in the restrictive-fluid group and 51 of 784 patients (6.5%) in the standard-fluid group (Table S2).

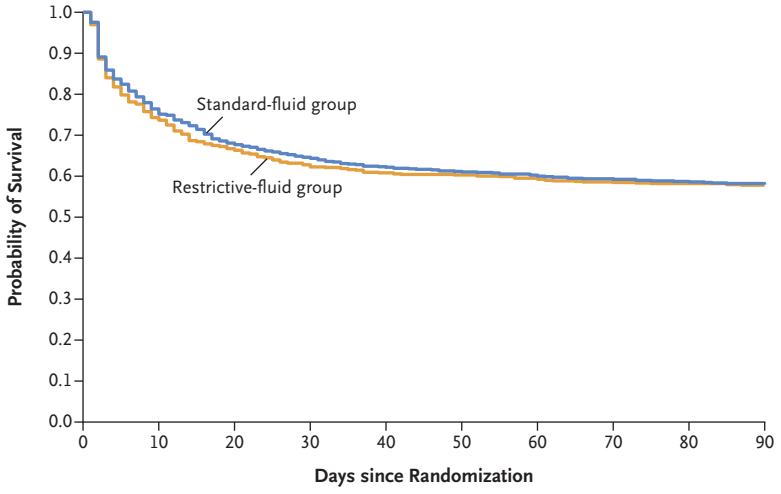
Figure 2 (facing page). Overall Survival and Absolute Difference in Death at 90 Days.

Panel A shows the survival curves censored at day 90 for the two groups in the intention-to-treat population. For one patient in each group, consent was not obtained for the collection of date of death, and those patients are not included. Four patients who were lost to 90-day follow-up (three patients in the restrictive-fluid group and one in the standard-fluid group) were included in the survival curves until the last day they were known to be alive; at that time point, data from those patients were censored. Panel B shows adjusted absolute differences with 95% confidence intervals for the primary outcome measure of death at day 90 in the restrictive-fluid group as compared with the standard-fluid group in all patients and in the five predefined subgroups that were assessed with the use of logistic regression analysis after adjustment for the stratification variables. The size of each black box is proportional to the size of the corresponding subgroup. Respiratory support was defined as the use of invasive or noninvasive mechanical ventilation, including mask continuous positive airway pressure (CPAP) or CPAP through tracheostomy within the 24 hours before randomization. Acute kidney injury was defined as a modified classification of stage 2 or higher according to Kidney Disease: Improving Global Outcomes on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury.[18] A plasma lactate level higher than 4 mmol per liter (36 mg per deciliter) was recorded if measured in any plasma sample that was obtained within 3 hours before randomization. Patient weight was defined as body weight in kilograms at the time of randomization (measured or estimated). Intravenous (IV) fluid volume at randomization included the volume of all crystalloid fluids, colloid fluids, and blood products the patient had received within the 24 hours before undergoing randomization, independent of the location where the fluids were administered, and included IV fluids with medication and nutrition. Full descriptions of the subgroups are available in the Supplementary Appendix. A P value of less than 0.01 was considered to indicate statistical significance in the subgroup analyses.

INTRAVENOUS FLUID INTERVENTION

During the 90-day trial period, the median cumulative volume of intravenous fluids administered in the ICU, excluding fluids administered with medication and nutrition, was 1798 ml in the restrictive-fluid group and 3811 ml in the standard-fluid group (Table 2, and Figs. S1 and S2). The median cumulative volume of all fluids given in the ICU was 10,433 ml in the restrictive-fluid group and 12,747 ml in the standard-fluid group (Table 2 and Table S3). The median cumu-

A Overall Survival

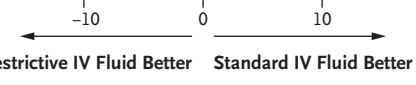


No. at Risk

Standard-fluid group	780	596	531	504	486	477	470	463	458	454
Restrictive-fluid group	763	567	509	479	464	460	454	447	444	441

B Death at 90 Days

Subgroup	Restrictive-Fluid Group	Standard-Fluid Group	Absolute Percentage Point Difference (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients			
All patients	323/764	329/781	0.1 (−4.7 to 4.9)	
Respiratory support				0.03
Yes	184/396	196/377	−5.1 (−11.3 to 1.6)	
No	138/385	132/399	5.7 (−1.4 to 12.4)	
Acute kidney injury				0.57
Yes	146/309	169/360	−0.8 (−8.0 to 6.7)	
No	174/439	158/411	2.0 (−4.6 to 8.4)	
Plasma lactate				0.65
>4.0 mmol/liter	164/337	180/366	−0.5 (−7.5 to 6.5)	
≤4.0 mmol/liter	158/416	148/409	1.7 (−5.1 to 8.1)	
Body weight				0.34
≥76 kg	164/401	163/425	2.5 (−4.1 to 9.0)	
<76 kg	158/352	165/350	−2.2 (−9.1 to 4.8)	
IV fluid volume at randomization				0.15
≥30 ml/kg body weight	208/493	230/515	−2.1 (−8.1 to 3.7)	
<30 ml/kg body weight	114/260	98/260	5.3 (−3.1 to 13.5)	



lative fluid balance was 1645 ml in the restrictive-fluid group and 2368 ml in the standard-fluid group. The intravenous fluid protocol was violated in the cases of 162 patients (21.5%) in the restrictive-fluid group and 101 patients (13.0%) in the standard-fluid group (Table S4).

OUTCOMES

At 90 days after randomization, death had occurred in 323 of 764 patients (42.3%) in the restrictive-fluid group and 329 of 781 patients (42.1%) in the standard-fluid group (adjusted absolute difference, 0.1 percentage points; 95% confidence interval [CI], −4.7 to 4.9; P=0.96) (Table 3 and Fig. 2). The results of the sensitivity analysis were consistent with those of the primary analysis after adjustment for risk factors at baseline; the results were also consistent with those of the per-protocol analysis (Table S5). In the predefined subgroup analyses, there was no

significant heterogeneity in the intervention effect on mortality at 90 days (Fig. 2).

At 90 days after randomization, one or more serious adverse events had occurred in 221 of 751 (29.4%) patients in the restrictive-fluid group and 238 of 772 patients (30.8%) in the standard-fluid group (adjusted absolute difference, −1.7 percentage points; 99% CI, −7.7 to 4.3) (Table 3). After the administration of intravenous crystalloid fluids, one or more serious adverse reactions occurred in 31 of 755 patients (4.1%) in the restrictive-fluid group and 32 of 776 patients (4.1%) in the standard-fluid group (adjusted absolute difference, −0.1 percentage points; 99% CI, −2.8 to 2.6) (Table S6). The numbers of days alive without life support and days alive and out of the hospital at 90 days were similar in the two groups (Figs. S3 and S4).

DISCUSSION

In this international, randomized clinical trial involving adult patients with septic shock in the ICU, we observed no significant differences in 90-day mortality or serious adverse events among the patients who received restricted fluid therapy and those who received standard therapy. The patients in the two groups also had similar survival durations without life support and after hospital discharge at 90 days. The 95% confidence interval for the difference in 90-day mortality between the restrictive-fluid and standard-fluid groups suggested that an absolute increase or decrease of 5 percentage points or more was unlikely.

Our results add to the findings in a recent systematic review of randomized trials of lower fluid volumes as compared with higher fluid volumes in patients with sepsis. In the meta-analysis of the included trials, there was no significant difference between the groups in mortality; however, only 621 patients were included in those trials.[12] Our results may contrast with those of some observational studies on this topic, the majority of which have suggested harm from higher fluid volumes as compared with lower fluid volumes in patients with sepsis.[3] However, confounding by indication and time-dependent exposure might have biased the observational studies.

The strengths of our trial include the high completeness of the data and the enrollment of patients who had characteristics and outcomes that were similar to those observed in other trials involving patients with septic shock.[7,19,20,30] Fluid volumes in the standard-fluid group were within the ranges of those observed in recent trials of fluid types used to treat patients in the ICU.[31,32] It is reasonable to assume that our results are generalizable, at least within Europe, because patients were recruited from 31 university and non-university ICUs in eight European countries, and most patients who were screened were included in the trial. We conducted a pilot trial that tested part of the trial protocol before conducting the present trial,[7] and the protocol was intended to be feasible and designed to permit staff members at all the trial centers to follow routine practice, except for the administration of intravenous fluids.

Our study has several limitations. Patients and personnel were aware of group assignments. Data regarding some important co-interventions and hemodynamic factors were not collected. Patients had received some fluid before enrollment, some protocol violations occurred, and most fluid was given outside the volumes specified by the protocol, all of which were issues that might have affected the results. Different results may be obtained in settings where more intravenous fluid is used in standard care. We had limited power to detect differences in some outcomes and in the subgroup analyses. Finally, our statistical goal of detecting an absolute between-group difference of 7 percentage points in 90-day mortality may be considered large.[33] Among adult patients in the ICU with septic shock, intravenous fluid restriction did not result in fewer deaths at 90 days than standard intravenous fluid therapy.

Supported by a grant (NNF17OC0028608) from the Novo Nordisk Foundation and by the Sofus Friis' Foundation, the Rigshospitalets Research Council, and the Danish Society of Anesthesiology and Intensive Care Medicine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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