

## ORIGINAL ARTICLE

# Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

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## ABSTRACT

**BACKGROUND**

The safety and efficacy of hydroxyethyl starch (HES) for fluid resuscitation have not been fully evaluated, and adverse effects of HES on survival and renal function have been reported.

**METHODS**

We randomly assigned 7000 patients who had been admitted to an intensive care unit (ICU) in a 1:1 ratio to receive either 6% HES with a molecular weight of 130 kD and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization. The primary outcome was death within 90 days. Secondary outcomes included acute kidney injury and failure and treatment with renal-replacement therapy.

**RESULTS**

A total of 597 of 3315 patients (18.0%) in the HES group and 566 of 3336 (17.0%) in the saline group died (relative risk in the HES group, 1.06; 95% confidence interval [CI], 0.96 to 1.18;  $P=0.26$ ). There was no significant difference in mortality in six predefined subgroups. Renal-replacement therapy was used in 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45;  $P=0.04$ ). In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively ( $P=0.005$ ), and renal failure occurred in 10.4% and 9.2% of patients, respectively ( $P=0.12$ ). HES was associated with significantly more adverse events (5.3% vs. 2.8%,  $P<0.001$ ).

**CONCLUSIONS**

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy. (Funded by the National Health and Medical Research Council of Australia and others; CHEST ClinicalTrials.gov number, NCT00935168.)

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\*Investigators in the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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THE ADMINISTRATION OF INTRAVENOUS fluids to increase intravascular volume is a frequent intervention in the intensive care unit (ICU), but the choice of resuscitation fluid remains controversial.<sup>1,2</sup> Globally, 0.9% sodium chloride (saline) is the most commonly used fluid, although colloids are administered as often as crystalloids, and hydroxyethyl starch (HES) is the most frequently used colloid.<sup>3</sup>

Several studies have questioned the safety of HES in critically ill patients, with particular concern that its use increases the risk of acute kidney injury.<sup>4,5</sup> Most concern has focused on the use of concentrated HES solutions (10%) with a molecular weight of more than 200 kD and a molar substitution ratio (the number of hydroxyethyl groups per glucose molecule) of more than 0.5.<sup>4,6</sup> Commonly used HES solutions have a lower concentration (6%) with a molecular weight of 130 kD and molar substitution ratios of 0.38 to 0.45. These preparations are available in different crystalloid carrier solutions. The clinical effects of lower-molecular-weight HES solutions have not been fully evaluated either in large clinical trials or in the broad range of ICU patients to whom they are now commonly administered.<sup>7</sup> Additional concern arose from a recent Scandinavian trial reporting that the use of 6% HES (130/0.42) significantly increased mortality in patients with severe sepsis and septic shock.<sup>8</sup>

We conducted a large-scale, randomized, controlled trial to evaluate the safety and efficacy of 6% HES (130/0.4) in 0.9% saline as compared with 0.9% saline alone for fluid resuscitation in a heterogeneous population of adult patients treated in the ICU.

## METHODS

### STUDY OVERSIGHT

The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) was an investigator-initiated, multicenter, prospective, blinded, parallel-group, randomized, controlled trial conducted in 32 hospitals in Australia and New Zealand.

The study-management committee designed the trial. The trial was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group. The study protocol<sup>9</sup> (available with the full text of this article at NEJM.org) was approved by the human research ethics committee at the Northern Sydney and Central Coast Area Health Service, the ethics committee

at the University of Sydney, and by each participating institution. Written informed consent before randomization or delayed consent was obtained from each patient, legal surrogate, or institutional ethics committee.

The statistical analysis plan<sup>10</sup> was reported previously. Statistical analyses were conducted at the George Institute for Global Health. The authors vouch for the data and statistical analyses, made the decision to submit the manuscript for publication, and assume responsibility for the fidelity of the final report to the protocol.

The study was funded by a project grant from the National Health and Medical Research Council of Australia and by unrestricted grants from the New South Wales Ministry of Health and Fresenius Kabi, the manufacturer of Voluven. Funding agencies had no input into the design, conduct, data collection, statistical analysis, or writing of the manuscript. Fresenius Kabi supplied the study fluids and distributed them to participating sites.

Independent analysis of the concentration and degree of molar substitution of HES and the concentration of saline was obtained for a random sample of 20 bags with the use of gravimetric analysis and nuclear magnetic resonance spectroscopy (Chemical Analysis).

### PATIENTS

Patients who were 18 years of age or older were assessed for eligibility on admission to the ICU. Patients who met the eligibility criteria were those whom the treating clinician judged to require fluid resuscitation, which was defined as the administration of a bolus of intravenous fluid over and above that required for maintenance or replacement fluids. Fluid was administered to correct hypovolemia at any time during the patient's ICU admission, as determined by the treating clinician and supported by at least one objective physiological criterion (Table S1A in the Supplementary Appendix, available at NEJM.org). The treating clinicians determined the initial and subsequent volumes and the rate of administration of resuscitation fluid, depending on clinical signs and the subsequent response to fluid administration.

Patients who had received more than 1000 mL of HES before screening, those with impending or current dialysis-dependent renal failure, and those with evidence of intracranial hemorrhage on cranial computed tomography were excluded.

A full list of exclusion criteria is provided in Table S1B in the Supplementary Appendix.

# **STUDY RANDOMIZATION AND TREATMENT**

Study treatments were randomly assigned over an encrypted Web-based randomization system with the use of a minimization algorithm stratified according to institution and an admission diagnosis of trauma.

Patients were assigned to receive either 6% HES (130/0.4) in 0.9% saline (Voluven, Fresenius Kabi) or 0.9% saline in indistinguishable Freeflex 500-ml bags<sup>9</sup> for all fluid resuscitation in the ICU until discharge, death, or 90 days after randomization.

In accordance with registration by the Therapeutic Goods Administration of Australia and the New Zealand Medicines and Medical Devices Safety Authority for 6% HES (130/0.4), study fluid was administered to a maximum dose of 50 ml per kilogram of body weight per day, followed by open-label 0.9% saline for the remainder of the 24-hour period.

Study fluid was stopped in patients who were treated with any mode of renal-replacement therapy. In these patients, treatment with saline was recommended, but any other fluid, apart from HES, was permitted. The administration of resuscitation fluids outside the ICU was not controlled.

All other aspects of patient care, including maintenance fluids and nutrition, cardiovascular monitoring, pharmacologic support, and respiratory and renal support, were conducted at the discretion of the treating clinicians.

# **OUTCOME MEASURES**

The primary outcome measure was all-cause mortality 90 days after randomization.

Secondary outcomes within the 90-day follow-up period were the incidence of acute kidney injury, as defined with the use of a five-category scoring system to evaluate risk, injury, failure, loss, and end-stage kidney injury (RIFLE)<sup>11</sup>; the use of renal-replacement therapy; new organ failures for cardiovascular, respiratory, coagulation, and liver systems that were not present at baseline; duration of mechanical ventilation and renal-replacement therapy; and cause-specific mortality.

Using the RIFLE diagnostic criteria, we evaluated patients for being at risk for kidney dysfunction (RIFLE-R), for injury to the kidney

(RIFLE-I), and for failure of kidney function (RIFLE-F) on the basis of incremental increases in serum creatinine levels from baseline and decreases in urine output over specified time periods. Patients with a complete loss of kidney function for more than 4 weeks (RIFLE-L) and end-stage kidney disease (RIFLE-E) completed the diagnostic criteria (Table S2 in the Supplementary Appendix). Included in the analysis was any mode of renal-replacement therapy that was prescribed by the attending physician. New organ failures for cardiovascular, respiratory, coagulation, and liver systems that were not present at baseline were defined by a score of 3 or more on the Sequential Organ Failure Assessment (SOFA),<sup>12</sup> which ranges from 0 to 4 for each of six organ systems, including neurologic and renal systems, with higher scores indicating more severe organ dysfunction (Table S3 in the Supplementary Appendix).

Tertiary outcomes were the duration of ICU stay and hospital admission and the rate of death in the ICU and hospital.

The primary outcome was also examined in six subgroup pairs on the basis of baseline characteristics: the presence or absence of diagnostic criteria for urine output for acute kidney injury (RIFLE-R and RIFLE-I categories), the presence or absence of sepsis at randomization,<sup>13</sup> the presence or absence of trauma with or without traumatic brain injury, the score (<25 vs. ≥25) on the Acute Physiology and Chronic Health Evaluation (APACHE) II<sup>14</sup> (ranging from 0 to 71, with higher scores indicating an increased risk of death), and receipt or nonreceipt of HES before randomization.

# **DATA AND STUDY MANAGEMENT**

Trained research coordinators collected data at each site and entered them into a Web-based database. Data monitoring and source data verification were conducted according to a prespecified monitoring plan. An independent data and safety monitoring committee reviewed data from prespecified interim analyses after the enrollment of 2000 and 4000 patients.

# **STATISTICAL ANALYSIS**

We determined that a sample size of 7000 patients would provide a power of 90% to detect an absolute difference of 3.5 percentage points in 90-day mortality on the basis of an estimated baseline mortality of 26% at an alpha level of 0.05 with an

assumption of a 5% loss to follow-up.<sup>10</sup> In addition, the study had a power of 90% with an alpha level of 0.05 to detect an absolute increase in the relative risk of acute kidney injury of 1.5 percentage points from a baseline incidence of 6%.<sup>4</sup>

We conducted all analyses on an intention-to-treat basis. Methods for the handling of missing data are outlined in the Supplementary Appendix. We compared binary outcomes using relative risks with 95% confidence intervals and chi-square tests. Continuous outcomes were compared with the use of mean differences and unpaired t-tests. Adjusted analyses were performed with the use of robust Poisson regression for binary outcomes and robust linear regression for continuous outcomes. Baseline covariates included the presence or absence of trauma, age, ICU admission source, APACHE II score, and baseline serum creatinine level. We compared survival times using log-rank tests and present these as Kaplan–Meier curves. Comparisons of fluid and physiological data averaged over the first 4 days were performed with the use of t-tests.

For the predefined subgroups, we assessed the primary outcome using methods similar to those used for the main analysis, and we assessed heterogeneity of treatment effects among subgroup pairs using the test for a common relative risk. We conducted post hoc analyses comparing changes in serum creatinine levels and urine output during the first 7 days in each group and in patients who satisfied the diagnostic criteria for RIFLE-R, RIFLE-I, and RIFLE-F categories of acute kidney injury. All analyses were conducted with the use of SAS statistical software, version 9.2 (SAS Institute).

## RESULTS

### PATIENTS

From December 2009 through January 2012, we enrolled 7000 patients in 32 adult medical–surgical ICUs in Australia and New Zealand, with 3500 patients assigned to receive 6% HES (130/0.4) in 0.9% saline (HES group) and 3500 to receive 0.9% saline (saline group) (Fig. 1). The two groups of patients had similar characteristics at baseline (Table 1). The primary outcome was available for 3315 patients (94.7%) in the HES group and 3336 patients (95.3%) in the saline group.

### FLUID THERAPY AND TREATMENT EFFECTS

Independent analysis of the random sample of study fluids reported the concentration of HES to be between 5.97% and 6.00%, with a mean degree of molar substitution of 0.44. The concentration of saline in the HES bags was between 0.92% and 0.93%.

During the first 4 days, the HES group received significantly less study fluid than the saline group (mean [ $\pm$ SD] daily average, 526 $\pm$ 425 ml vs. 616 $\pm$ 488 ml;  $P<0.001$ ), with most of the volume administered in the first 24 hours (Fig. S1 in the Supplementary Appendix).

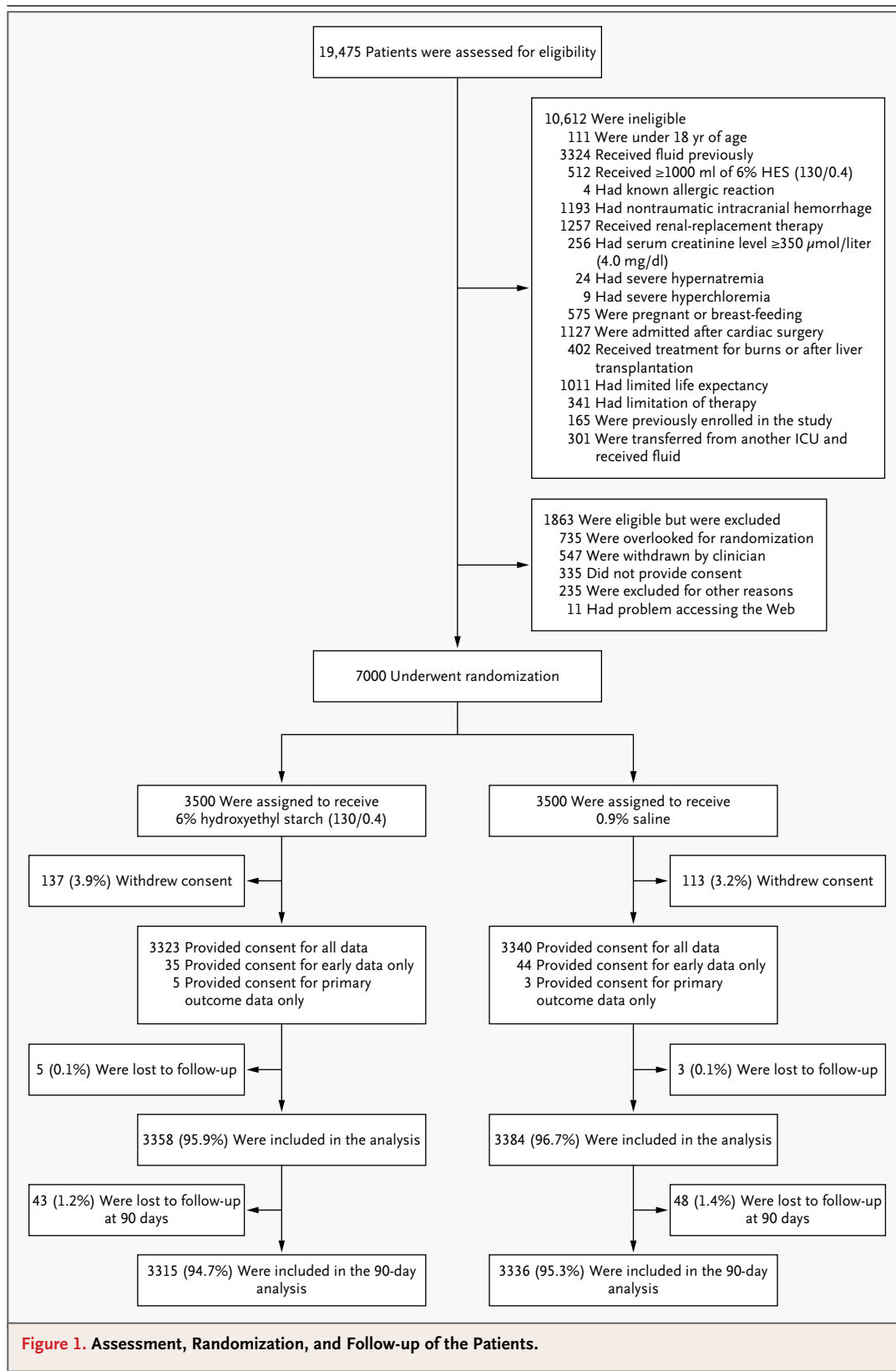
The HES group also received significantly less nonstudy fluid than the saline group (851 $\pm$ 675 ml vs. 1115 $\pm$ 993 ml,  $P<0.001$ ), resulting in a significantly lower positive net fluid balance (921 $\pm$ 1069 ml vs. 982 $\pm$ 1161 ml,  $P=0.03$ ) (Table S4 and Fig. S1 in the Supplementary Appendix).

During the first 4 days, the HES group received significantly more blood products than the saline group (78 $\pm$ 250 ml vs. 60 $\pm$ 190 ml,  $P<0.001$ ), and central venous pressure was significantly higher in the HES group (11.3 $\pm$ 4.8 mm Hg vs. 10.4 $\pm$ 4.4 mm Hg,  $P<0.001$ ) (Fig. S1 and S2 in the Supplementary Appendix). There were no significant between-group differences in heart rate, mean arterial pressure, and lactate levels during the first 4 days (Fig. S2 in the Supplementary Appendix).

### OUTCOMES

In the HES group, 597 of 3315 patients (18.0%) died within 90 days after randomization, as compared with 566 of 3336 patients (17.0%) in the saline group (relative risk in the HES group, 1.06; 95% confidence interval [CI], 0.96 to 1.18;  $P=0.26$ ) (Table 2). There was no significant difference in the probability of survival between the HES group and the saline group during the 90 days after randomization ( $P=0.27$ ) (Fig. 2A). There was no significant heterogeneity in the effect of treatment on 90-day mortality in any of the predefined subgroups (Fig. 2B). Renal-replacement therapy was administered to 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 patients (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45;  $P=0.04$ ).

The diagnostic criteria for being at risk for various stages of renal injury were as follows: renal dysfunction (RIFLE-R), 1788 of 3309 pa-



**Figure 1. Assessment, Randomization, and Follow-up of the Patients.**

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	HES (N=3358)	Saline (N=3384)
Age — yr	63.1±17.0	62.9±16.9
Male sex — no./total no. (%)	2030/3356 (60.5)	2041/3384 (60.3)
Weight — kg	79.4±21.0	78.6±20.8
Source of admission to ICU — no./total no. (%)		
Emergency department	930/3353 (27.7)	931/3379 (27.6)
Hospital floor	659/3353 (19.7)	668/3379 (19.8)
Another ICU	53/3353 (1.6)	41/3379 (1.2)
Another hospital	315/3353 (9.4)	306/3379 (9.1)
Operating room		
After emergency surgery	625/3353 (18.6)	630/3379 (18.6)
After elective surgery	771/3353 (23.0)	803/3379 (23.8)
Diagnosis on admission — no./total no. (%)		
Surgical cases	1426/3353 (42.5)	1450/3379 (42.9)
Nonsurgical cases	1920/3353 (57.3)	1926/3379 (57.0)
APACHE II score — median (interquartile range)†	17.0 (12.0–22.0)	17.0 (12.0–23.0)
Time from ICU admission to randomization — hr	10.9±156.5	11.4±165.4
Physiological variables		
Heart rate — beats/min	89.3±23.6	88.8±23.3
Mean arterial pressure — mm Hg	74.0±14.9	73.7±14.6
Central venous pressure — mm Hg	9.5±5.4	8.9±5.1
Lactate — mmol/liter	2.1±2.0	2.0±1.5
Mechanical ventilation — no./total no. (%)	2131/3326 (64.1)	2177/3354 (64.9)
Use of vasopressor — no./total no. (%)	1520/3337 (45.5)	1551/3361 (46.1)
Serum creatinine — μmol/liter	101.5±57.1	100.1±58.0
Urine output 6 hr before randomization — ml	453.5±418.3	426.6±422.9
Predefined subgroups — no./total no. (%)		
RIFLE criteria for acute kidney injury‡	522/1449 (36.0)	511/1421 (36.0)
Sepsis	979/3355 (29.2)	958/3376 (28.4)
Trauma	267/3358 (8.0)	265/3384 (7.8)
Traumatic brain injury	28/3338 (0.8)	30/3365 (0.9)
APACHE II score ≥25	597/3335 (17.9)	624/3356 (18.6)
Receipt of HES before randomization	509/3347 (15.2)	508/3372 (15.1)

\* Plus-minus values are means ±SD. There were no significant differences between the groups except for central venous pressure ( $P<0.001$ ) and lactate level ( $P<0.05$ ). To convert the values for creatinine to milligrams per deciliter, divide by 88.4. HES denotes hydroxyethyl starch, and ICU intensive care unit.

† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating an increased risk of death.

‡ RIFLE (risk, injury, or failure) criteria for acute kidney injury at baseline were calculated from measures of available urine output only in patients who satisfied the criteria for risk and injury. Changes in serum creatinine levels were not applicable.

tients (54.0%) in the HES group and 1912 of 3335 patients (57.3%) in the saline group (relative risk, 0.94; 95% CI, 0.90 to 0.98;  $P=0.007$ ); injury to the kidney (RIFLE-I), 1130 of 3265 patients (34.6%) in the HES group and 1253 of 3300 patients (38.0%) in the saline group (relative

**Table 2. Outcomes and Adverse Events.\***

Variable	HES	Saline	Relative Risk (95% CI)	P Value
<b>Outcome</b>				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03
Tertiary outcomes — no./total no. (%)				
Death in ICU	364/3313 (11.0)	360/3331 (10.8)	1.02 (0.89 to 1.17)	0.81
Death within 28 days	458/3313 (13.8)	437/3331 (13.1)	1.05 (0.93 to 1.19)	0.40
Death in hospital	483/3307 (14.6)	456/3324 (13.7)	1.06 (0.95 to 1.20)	0.30
<b>Mean Difference (95% CI)</b>				
Service utilization — no.				
Days in ICU	7.3±0.2	6.9±0.2	0.4 (0.0 to 0.9)	0.07
Days in hospital	19.3±0.3	19.1±0.3	0.2 (−0.8 to 1.1)	0.72
Days receiving mechanical ventilation	6.0±0.2	5.7±0.2	0.4 (−0.1 to 0.8)	0.12
Days receiving renal-replacement therapy	5.6±0.4	5.5±0.4	0.1 (−0.1 to 1.2)	0.86
<b>Treatment-related adverse events‡</b>				
Any event — no./total no. (%)	180/3416 (5.3)	95/3358 (2.8)		<0.001
Pruritus	137/3416 (4.0)	73/3358 (2.2)		
Skin rash	34/3416 (1.0)	16/3358 (0.5)		
Other	9/3416 (0.3)	6/3358 (0.2)		
Serious adverse events — no./total no. (%)§	2/3416 (0.1)	2/3358 (0.1)		0.98

\* Plus-minus values are means ±SE.

† New organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score<sup>12</sup> of at least 3 for each category in patients who did not have such organ failure at baseline.

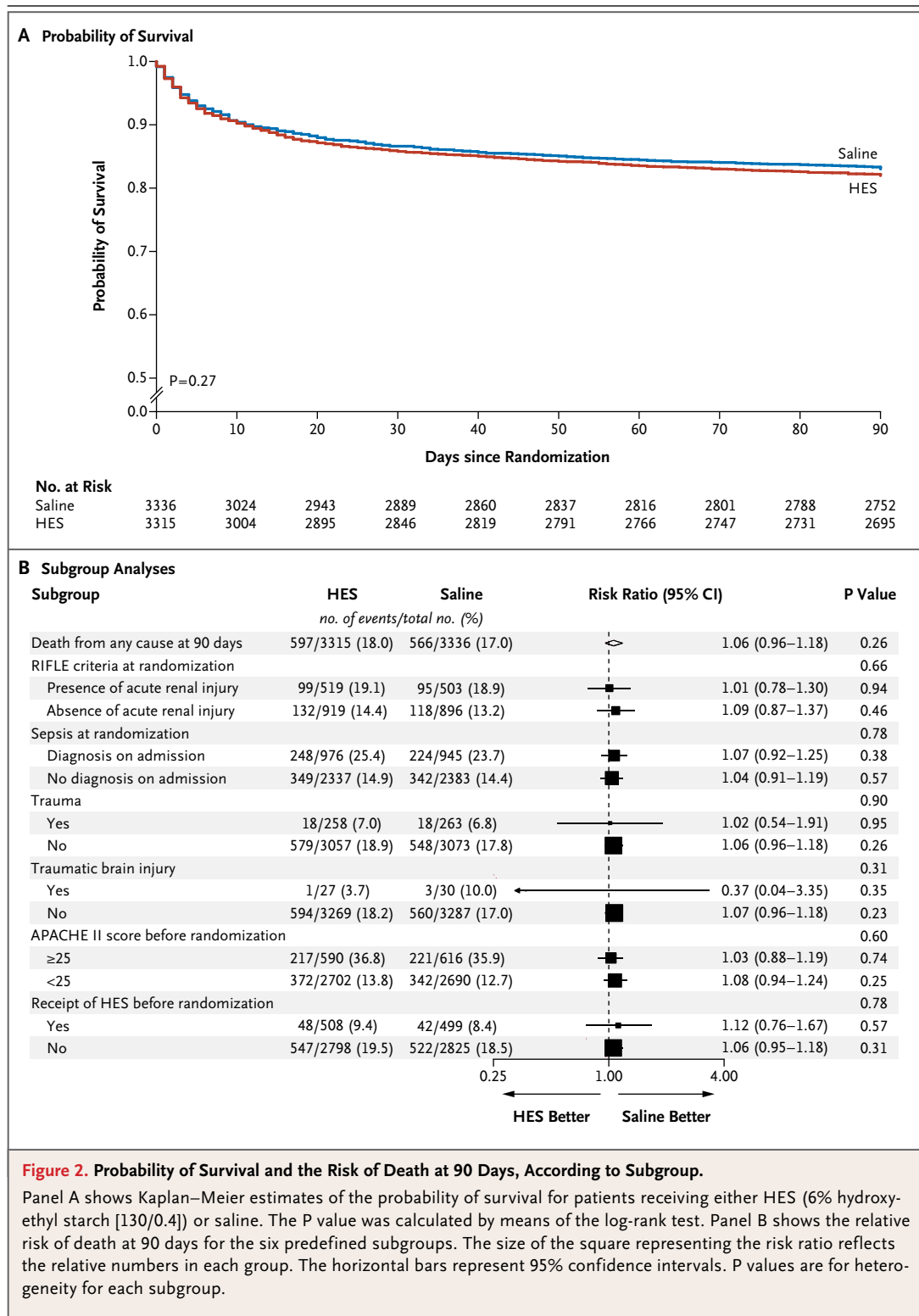
‡ Adverse events in the HES group include those in patients who received HES both before and after randomization.

§ Among the serious (nonfatal) treatment-related adverse events were one case each of anaphylactic shock and extravasation of fluid causing airway obstruction in the HES group and one case each of toxic epidermal necrolysis requiring unblinding of the study-group assignment and unexplained severe hypotension in the saline group.

risk, 0.91; 95% CI, 0.85 to 0.97; P=0.005); and failure of kidney function (RIFLE-F), 336 of 3243 patients (10.4%) in the HES group and 301 of 3263 patients (9.2%) in the saline group (relative risk, 1.12; 95% CI, 0.97 to 1.30; P=0.12).

Post hoc analysis showed that serum creati-

nine levels were significantly increased and urine output was significantly decreased in the HES group, as compared with the saline group, during the first 7 days (P=0.004 and 0.003, respectively) (Fig. 3). In addition, when the creatinine and urine-output components of each RIFLE catego-



ry were analyzed separately, the relative risks of meeting the criteria for the risk of kidney dysfunction (RIFLE-R) or kidney injury (RIFLE-I) were higher in the HES group than in the saline group (Fig. S3 in the Supplementary Appendix).

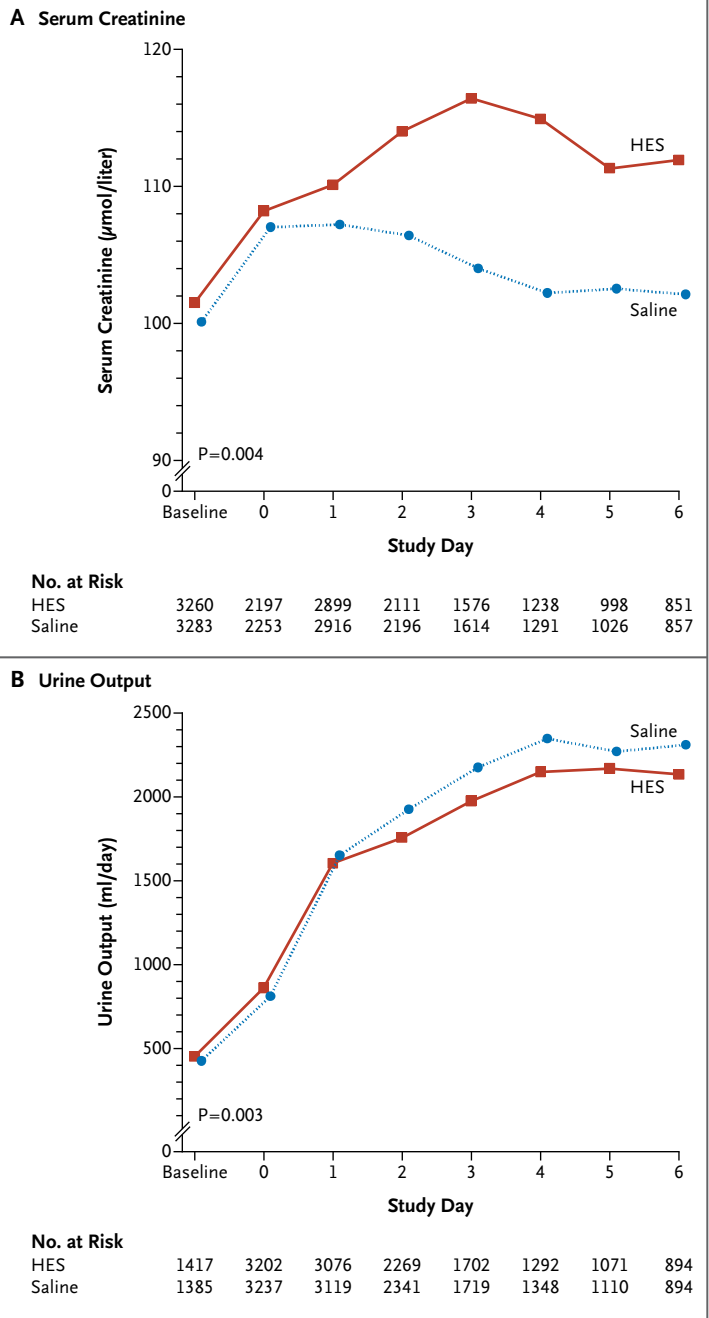
There was no significant between-group difference in rates of death in the ICU, at 28 days, and in the hospital or in rates of new respiratory or new coagulation organ failure. The incidence of new cardiovascular organ failure was significantly lower in the HES group than in the saline group (36.5% vs. 39.9%) (relative risk, 0.91; 95% CI, 0.84 to 0.99;  $P=0.03$ ). The incidence of new hepatic organ failure was significantly higher in the HES group than in the saline group (1.9% vs. 1.2%) (relative risk, 1.56; 95% CI, 1.03 to 2.36;  $P=0.03$ ). There were no significant differences in the duration of mechanical ventilation, of renal-replacement therapy, or of ICU or hospital stays between the two groups (Table 2). There was no significant between-group difference in cause-specific mortality within the 90-day follow-up period (Table S5 in the Supplementary Appendix). The main results were similar after adjustment for baseline covariates (Table S6 in the Supplementary Appendix).

The use of HES was associated with a significant increase in the rate of adverse events (5.3 vs. 2.8%,  $P<0.001$ ). Of these events, pruritus and rash were the most common (Table 2).

## DISCUSSION

In this randomized, controlled trial, there was no significant difference in mortality at 90 days in a heterogeneous population of ICU patients who received 6% HES (130/0.4) in 0.9% saline and those who received 0.9% saline alone for fluid resuscitation. The effect on mortality did not differ significantly in six predefined subgroup pairs.

Our study was a large-scale, pragmatic trial modeled on the Saline versus Albumin Fluid Evaluation (SAFE) trial.<sup>15</sup> We sought to minimize the risk of bias through centralized randomization, allocation concealment, and blinding of study-group assignments. We used a robust primary outcome measured at an interval relevant to this study population.<sup>16,17</sup> To further minimize the risk of bias, we published the statistical analysis plan,



**Figure 3. Serum Creatinine Levels and Urine Output through Day 6.**

Day 0 was defined as the day of randomization to the end of that day, which averaged 12 hours in the two study groups. P values are for the between-group comparisons of means of the individual daily averages for 7 days, including day 0. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

including predefined subgroups, before the unblinding of study-group assignments.<sup>10</sup>

A limitation of our study is that the observed rate of death was lower than predicted. This was due, in part, to the exclusion of patients with intracranial hemorrhage and those whom clinicians considered unlikely to survive, as well as the inclusion of patients who had undergone elective surgery. In addition, patients were recruited after admission to the ICU, when the requirements for fluid resuscitation are often less than those for patients in the emergency department or the operating room.

Despite these limitations, our trial had sufficient statistical power to detect an absolute mortality difference of 3 percentage points. Our results are consistent with a treatment effect that lies between a relative decrease of 4% or a relative increase of 18% in mortality arising from resuscitation with HES.

A fundamental reason for conducting our study was to determine whether currently used HES solutions increased the risk of acute kidney injury in ICU patients. Resuscitation with HES resulted in a 21% relative increase in the number of patients treated with renal-replacement therapy. Although criteria for the initiation of renal-replacement therapy were not outlined in the protocol and such therapy was initiated at the discretion of the attending clinicians, the clinicians were unaware of study-group assignments, which made it unlikely that the difference was caused by variations in thresholds for initiating therapy.<sup>18</sup>

The RIFLE score is a composite-end-point measure that combines effects on serum creatinine levels and urine output. In our study, the use of HES had opposite effects on the two components of this score, as compared with saline. Our post hoc analysis showed that treatment with HES was associated with increased urine output in patients with less severe acute kidney injury, which may have been due to increased intravascular volume or through a diuretic effect.<sup>19</sup> Conversely, serum creatinine levels were consistently higher in the HES group, suggesting a progressive reduction in creatinine clearance and more severe acute kidney injury.

The use of HES was associated with the administration of lower volumes of resuscitation fluid, although the ratio between HES and saline was similar to that observed in other blinded

trials, suggesting that the use of HES was not associated with a substantive volume-sparing effect.<sup>8,20,21</sup>

The use of HES was also associated with increased use of blood products and a decrease in the rate of new cardiovascular failure; the latter, as defined by the SOFA score, indicates a reduction in the use of vasopressors, which was most likely due to increased intravascular expansion. However, this rate reduction was not associated with differences in other resuscitation end points, such as mean arterial pressure or serum lactate levels. Conversely, the use of HES was associated with new hepatic failure, which as defined by the SOFA score indicates an increase in serum bilirubin levels.

The use of HES was associated with an increased incidence of adverse events, particularly pruritus and rash. Our observations are consistent with studies that have shown increased tissue accumulation of HES within the reticuloendothelial system, which is manifested cutaneously as pruritus<sup>22</sup> and may lead to acute kidney and hepatic injury.<sup>23,24</sup>

In studies involving patients with severe sepsis, HES was associated with increased mortality and acute kidney injury, resulting in the need for renal-replacement therapy.<sup>4,8</sup> The patients in our study were at lower risk for death than the patients in these studies, but the point estimate for an increased relative risk of death and acute kidney injury associated with HES was consistent with the effects seen in these trials.

In conclusion, our study does not provide evidence that resuscitation with 6% HES (130/0.4), as compared with saline, in the ICU provides any clinical benefit to the patient. Indeed, the use of HES resulted in an increased rate of renal-replacement therapy. Thus, the selection of resuscitation fluid in critically ill patients requires careful consideration of its safety, its potential effect on patient-centered outcomes, and its cost.

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