

## ORIGINAL ARTICLE

# Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

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## ABSTRACT

## BACKGROUND

Hydroxyethyl starch (HES) is widely used for fluid resuscitation in intensive care units (ICUs), but its safety and efficacy have not been established in patients with severe sepsis.

## METHODS

In this multicenter, parallel-group, blinded trial, we randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization.

## RESULTS

Of the 804 patients who underwent randomization, 798 were included in the modified intention-to-treat population. The two intervention groups had similar baseline characteristics. At 90 days after randomization, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate (relative risk, 1.17; 95% confidence interval [CI], 1.01 to 1.36;  $P=0.03$ ); 1 patient in each group had end-stage kidney failure. In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with renal-replacement therapy versus 65 patients (16%) assigned to Ringer's acetate (relative risk, 1.35; 95% CI, 1.01 to 1.80;  $P=0.04$ ), and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding (relative risk, 1.52; 95% CI, 0.94 to 2.48;  $P=0.09$ ). The results were supported by multivariate analyses, with adjustment for known risk factors for death or acute kidney injury at baseline.

## CONCLUSIONS

Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer's acetate. (Funded by the Danish Research Council and others; 6S ClinicalTrials.gov number, NCT00962156.)

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**I**NTRAVENOUS FLUIDS ARE THE MAINSTAY of treatment for patients with hypovolemia due to severe sepsis. Colloid solutions are used to obtain rapid and lasting circulatory stabilization, but there are limited data to support this practice.<sup>1</sup> The Surviving Sepsis Campaign guidelines recommend the use of either colloids or crystalloids,<sup>2</sup> but high-molecular-weight hydroxyethyl starch (HES) may cause acute kidney failure in patients with severe sepsis, as observed in two randomized trials.<sup>3,4</sup> Those trials had substantial limitations, and participants received HES solutions with a molecular weight of 200 kD and a substitution ratio (the number of hydroxyethyl groups per glucose molecule) of more than 0.4.<sup>3,4</sup> These solutions have largely been replaced by HES solutions with a lower molecular weight and a lower substitution ratio, HES 130/0.4.<sup>5,6</sup> There are limited data about the effects of HES 130/0.4 in patients with severe sepsis,<sup>7</sup> and its routine use has recently been discouraged.<sup>8</sup>

Given the lack of efficacy data and concerns about safety, we conducted the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial to evaluate the effects of HES 130/0.4 as compared with Ringer's acetate on the composite outcome of death or end-stage kidney failure in patients with severe sepsis.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

Patients were screened and underwent randomization between December 23, 2009, and November 15, 2011, in Denmark, Norway, Finland, and Iceland after the appropriate approvals. Patients were screened at 26 general intensive care units (ICUs) in 13 university and 13 nonuniversity hospitals. Written informed consent was obtained from patients or their legal surrogates before enrollment. In all cases, consent was obtained from the patient when possible. If consent was withdrawn or not granted, we asked the patient or surrogate for permission to continue registration of trial data and to use these data in the analyses. The protocol, including details on trial conduct and procedures and the statistical analysis plan, has been published previously<sup>9</sup> and is available with the full text of this article at NEJM.org. B. Braun Medical provided trial fluids to all trial sites free of charge. Neither the funders nor B. Braun Medical had influence on the protocol, trial conduct, or data analyses or reporting. The steering com-

mittee vouches for the accuracy and completeness of the data and the analysis and the fidelity of the study to the protocol, and it made the decision to submit the manuscript for publication. The writing committee had full access to all data and wrote the manuscript with input from all authors. The trial was endorsed by the European Clinical Research Infrastructures Network.

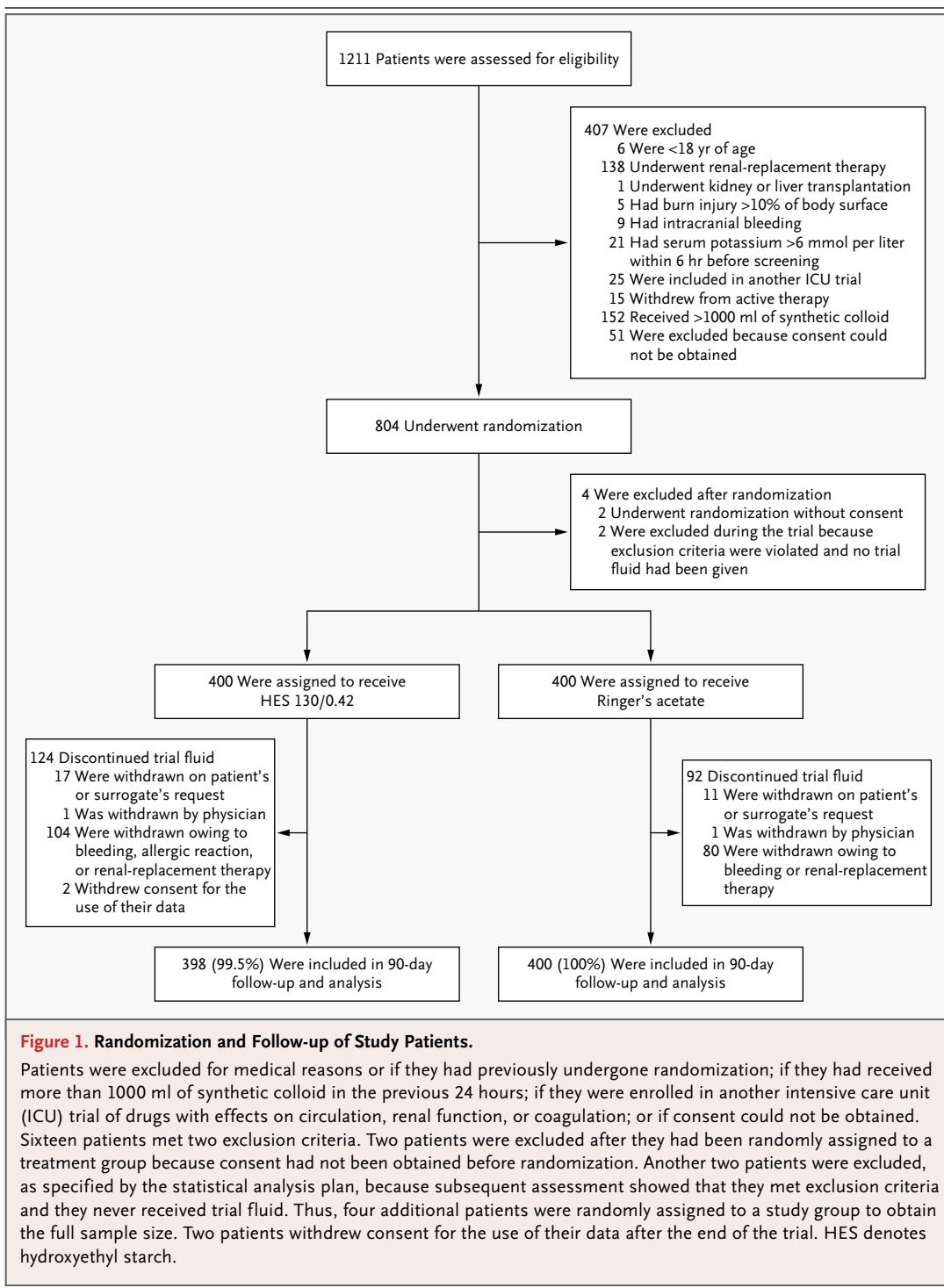
This trial was an investigator-initiated, multicenter, blinded, stratified, parallel-group clinical trial with a computer-generated allocation sequence and centralized, blinded randomization. We randomly assigned patients with severe sepsis in a 1:1 ratio to fluid resuscitation with either HES 130/0.42 or Ringer's acetate. Treatment assignments were concealed from patients, clinicians, research staff, the data monitoring and safety committee, the statistician, and the writing committee when it wrote the first draft for the abstract (for details, see the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to the presence or absence of shock, the presence or absence of active hematologic cancer, and admission to a university or nonuniversity hospital, because these characteristics might have influenced the outcome.<sup>10,11</sup> The conduct of the trial and the safety of the participants were overseen by the data monitoring and safety committee, which performed an interim analysis after 400 patients had undergone randomization.

### PATIENTS

We screened patients 18 years of age or older who needed fluid resuscitation in the ICU, as judged by the ICU clinicians, and who fulfilled the criteria for severe sepsis within the previous 24 hours<sup>12</sup> (for details, see the Supplementary Appendix). Patients were excluded for the reasons shown in Figure 1.

### INTERVENTIONS

Trial fluid (6% HES 130/0.42 in Ringer's acetate [Tetraspan 6%, B. Braun] or Ringer's acetate [Sterofundin ISO, B. Braun]; see the Supplementary Appendix for electrolyte content) was used when ICU clinicians judged that volume expansion was needed in the ICU for a maximum of 90 days. Trial fluid was delivered in identical bags (Ecobag, B. Braun), which were fully covered in custom-made black, opaque plastic bags and sealed by staff members who were not involved in data registration or patient care. The maximum daily dose



was 33 ml per kilogram of ideal body weight (for details, see the Supplementary Appendix). If doses higher than the maximum daily dose were required, unmasked Ringer's acetate was used, regardless of the treatment assignment. In the event

of severe bleeding, a severe allergic reaction, or the commencement of renal-replacement therapy for acute kidney injury, trial fluid was permanently stopped and 0.9% saline or Ringer's lactate was given for volume expansion in the ICU until

90 days after randomization. All other interventions were at the discretion of the ICU clinicians, and crystalloid and albumin solutions were allowed for indications other than volume expansion. Criteria for renal-replacement therapy were not included in the protocol.

#### OUTCOMES

The composite primary outcome was death or dependence on dialysis 90 days after randomization<sup>13</sup>; the latter was defined as the use of any renal-replacement therapy during the period from 86 to 94 days after randomization. In addition, these outcomes were analyzed separately. Secondary outcomes were death at 28 days; death at the time of the latest follow-up assessment; severe bleeding (defined as clinical bleeding that required 3 or more units of packed red cells within 24 hours)<sup>14</sup> while the patient was in the ICU; severe allergic reactions; the score on the Sepsis-related Organ Failure Assessment (SOFA), modified by excluding the Glasgow Coma Scale (Table S9 in the Supplementary Appendix),<sup>15</sup> at day 5 after randomization (the SOFA score includes subscores ranging from 0 to 4 for each of five components [circulation, lungs, liver, kidneys, and coagulation], with higher scores indicating more severe organ failure); the development of acute kidney injury (use of renal-replacement therapy or a renal SOFA score of 3 or higher after the patient had a renal SOFA score of 2 or lower at randomization) in the ICU after randomization; doubling of the plasma creatinine level in the ICU after randomization<sup>3,4</sup>; acidosis (arterial pH <7.35) in the ICU; and percentages of days alive without renal-replacement therapy, days alive without mechanical ventilation, and days alive out of the hospital in the 90 days after randomization.

Data for the outcome measures were obtained by the 6S trial investigators or their delegates from patient files, national registries, and telephone contact with patients and hospitals for the 90-day follow-up period (not limited to the index admission). The final mortality follow-up was conducted on February 16, 2012, which was 90 days after randomization of the last patient.

#### STATISTICAL ANALYSIS

We calculated that we would need to enroll 800 patients for the study to have 80% power to show an absolute between-group difference of 10 percentage points in the primary outcome measure

at a two-sided alpha level of 0.05, assuming a 45% mortality rate<sup>6,16</sup> and a 5% rate of dependence on dialysis at 90 days.<sup>17,18</sup> During the trial, four patients were excluded after randomization (two for whom consent had not been obtained and two who met exclusion criteria and never received trial fluid). Four additional patients were randomly assigned to a study group to obtain the full sample (Fig. 1).<sup>19</sup>

All analyses were performed by one of the authors before the breaking of the randomization code, according to International Conference on Harmonization—Good Clinical Practice guidelines<sup>20</sup> and the statistical analysis plan. The analyses were performed on data from the modified intention-to-treat population, defined as all randomly assigned patients except those who could be excluded without the risk of bias (four patients who underwent randomization by mistake and who never received trial fluid)<sup>19</sup> and those for whom we did not have consent for the use of data (two patients) (Fig. 1). In the per-protocol analyses, patients with one or more major protocol violations were excluded; see the Supplementary Appendix for definitions of the trial populations.

Data were analyzed with the use of unadjusted chi-square tests for binary outcome measures and Wilcoxon signed-rank tests for rate and ordinal data. We also compared the primary outcome in the per-protocol populations and in the predefined subgroups (patients with shock or acute kidney injury at the time of randomization) and used multiple logistic-regression analyses in the modified intention-to-treat population to adjust for differences in baseline variables, including known risk factors for death or acute kidney injury. Details on the handling of missing data are given in the Supplementary Appendix. All analyses were performed with the use of SAS software, version 9.3. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

#### STUDY POPULATION

The 798 patients — 398 in the HES 130/0.42 group (hereafter called the starch group) and 400 in the Ringer's acetate group (Fig. 1) — were followed for at least 90 days and analyzed in the group to which they were assigned. Baseline characteristics were similar in the two groups (Table 1, and Table S1 in the Supplementary Appendix).

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

Characteristic	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)
Age — yr		
Median	66	67
Interquartile range	56–75	56–76
Male sex — no. (%)	239 (60)	244 (61)
Ideal body weight — kg†		
Median	72	72
Interquartile range	60–80	60–80
Admitted to university hospital — no. (%)	194 (49)	188 (47)
Surgery — no. (%)‡		
Emergency	114 (29)	116 (29)
Elective	34 (9)	48 (12)
Source of ICU admission — no. (%)		
Emergency department	109 (27)	94 (24)
General ward	177 (44)	196 (49)
Operating or recovery room	59 (15)	54 (14)
Other ICU in the same hospital	21 (5)	14 (4)
Other hospital	32 (8)	42 (10)
Source of sepsis — no. (%)§		
Lungs	212 (53)	229 (57)
Abdomen	130 (33)	133 (33)
Urinary tract	56 (14)	50 (12)
Soft tissue	38 (10)	46 (12)
Other	43 (11)	33 (8)
SAPS II — median (interquartile range)¶	50 (40–60)	51 (39–62)
SOFA score — median (interquartile range)	7 (5–9)	7 (5–9)
Shock — no. (%)**	336 (84)	337 (84)
Acute kidney injury — no. (%)††	142 (36)	140 (35)
Mechanical ventilation — no. (%)	240 (60)	245 (61)

\* None of the differences between the two groups were significant ( $P>0.05$ ). The values for the Simplified Acute Physiology Score (SAPS)<sup>21</sup> II, Sepsis-related Organ Failure Assessment (SOFA)<sup>15</sup> score, acute kidney injury, and mechanical ventilation (invasive or noninvasive) pertain to the 24 hours before randomization. For additional baseline characteristics, see Table S1 in the Supplementary Appendix. HES denotes hydroxyethyl starch, and ICU intensive care unit.

† Ideal body weight was calculated as estimated height in centimeters minus 100 for men and estimated height in centimeters minus 105 for women.

‡ Data are shown for patients who underwent surgery during the index hospitalization but before randomization.

§ Some patients had more than one source of infection. The “other” category included sepsis from a vascular catheter-related infection, meningitis, or endocarditis, as well as sepsis from unknown sources.

¶ SAPS II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease. Data regarding 1 or 2 of the 17 variables were missing for 105 patients in the HES 130/0.42 group and 108 patients in the Ringer's acetate group, so the scores for these patients are not included here.

|| The SOFA score includes subscores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure (Table S9 in the Supplementary Appendix). The scoring was modified because cerebral failure was not assessed. One of the five subscores was missing for two patients in the HES 130/0.42 group, so their scores are not included here.

\*\* Shock at randomization was defined as a mean arterial pressure of less than 70 mm Hg, the need for ongoing treatment with vasopressor or inotropic agents, or a plasma lactate level of more than 4.0 mmol per liter in the hour before randomization.

†† Acute kidney injury was defined as a renal SOFA score of 2 or higher (plasma creatinine level >1.9 mg per deciliter [170 µmol per liter] or urinary output <500 ml per day).

## FLUID THERAPY, USE OF BLOOD PRODUCTS, AND CIRCULATORY EFFECTS

Of the 798 patients, 779 (98%) received trial fluid. The median cumulative volume of fluid received was 3000 ml (interquartile range, 1507 to 5100) in the starch group and 3000 ml (interquartile range, 2000 to 5750) in the Ringer's acetate group ( $P=0.20$ ), equaling 44 ml per kilogram of ideal body weight (interquartile range, 24 to 75) and 47 ml per kilogram (interquartile range, 25 to 76), respectively ( $P=0.18$ ). Seventy-seven patients (39 in the starch group and 38 in the Ringer's acetate group) received open-label synthetic colloids in the ICU during the 90-day trial period. Sixty-nine patients (28 in the starch group and 41 in the Ringer's acetate group) received trial fluid at doses higher than the protocol-specified maximum daily dose. Only 2 patients in the starch group received HES 130/0.42 at a dose higher than the maximum daily dose recommended by the manufacturer (50 ml per kilogram). Details on other fluid volumes and balances and protocol violations are provided in Table 2 and in the Supplementary Appendix, including Tables S2 and S3.

More patients in the starch group than in the Ringer's acetate group received blood products (relative risk, 1.20; 95% confidence interval [CI], 1.07 to 1.36;  $P=0.002$ ), including packed red cells (relative risk, 1.28; 95% CI, 1.12 to 1.47;  $P<0.001$ ) (Table 2, and Table S2 in the Supplementary Appendix). There were no significant differences between the two groups in the circulatory variables assessed at baseline and during the 24 hours after randomization (Table S4 in the Supplementary Appendix).

## OUTCOMES

The primary outcome, death or dependence on dialysis at 90 days after randomization, occurred in 202 patients (51%) in the starch group as compared with 173 patients (43%) in the Ringer's acetate group (relative risk, 1.17; 95% CI, 1.01 to 1.36;  $P=0.03$ ). One patient in each group was dependent on dialysis at day 90 (Table 3). Similar results were obtained in the multiple logistic-regression and per-protocol analyses (see the Supplementary Appendix, including Table S6). The survival curves for the two intervention groups are shown in Figure 2, and Figure S1 in the Supplementary Appendix. The two predefined subgroup analyses showed no heterogeneity in the effect of HES 130/0.42 on the primary outcome

in patients with shock or acute kidney injury at the time of randomization (Fig. 2).

More patients in the starch group than in the Ringer's acetate group received renal-replacement therapy (Table 3). Among all patients, renal-replacement therapy was associated with increased 90-day mortality (61%, vs. 44% for those not receiving renal-replacement therapy;  $P<0.001$ ). In the starch group, 38 patients (10%) had severe bleeding, as compared with 25 (6%) in the Ringer's acetate group (relative risk, 1.52; 95% CI, 0.94 to 2.48;  $P=0.09$ ) (Table 3).

The percentage of days alive without renal-replacement therapy and the percentage of days alive and out of the hospital were lower in the starch group than in the Ringer's acetate group (Table 3). None of the remaining secondary outcomes differed significantly between the groups (Table 3), but some of the post hoc analyses of kidney injury and bleeding showed significant differences (Tables S7 and S8 in the Supplementary Appendix).

## DISCUSSION

In this international, blinded, randomized trial of fluid resuscitation of patients with severe sepsis, HES 130/0.42 significantly increased the risk of death or dependence on dialysis at day 90, as compared with Ringer's acetate. The difference was due to an increased risk of death at 90 days, because only 1 patient in each group was dependent on dialysis at 90 days. HES 130/0.42 increased the absolute risk of death at 90 days by 8 percentage points, corresponding to a number needed to harm of 13. Similar results were observed in analyses adjusted for risk factors and in the subgroups of patients with shock or acute kidney injury at the time of randomization.

The increased risk of death observed with HES 130/0.42 in our trial is similar to that observed in the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial with HES 200/0.5,<sup>4</sup> but that trial was not powered to show the difference with statistical significance. The separation of the survival curves occurred around day 20 in both trials, indicating late deaths induced by HES. Both trials showed that HES was associated with impaired kidney function and increased use of renal-replacement therapy, the negative consequences of which are well known and were confirmed by our data.<sup>17,22</sup> In both trials,

**Table 2.** Fluid Therapy before and after Randomization.\*

Variable	HES 130/0.42 (N=398)			Ringer's Acetate (N=400)			P Value†	
	Patients	Volume Received‡		Patients	Volume Received‡			
		median	interquartile range		median	interquartile range		
	no./total no.§	ml		no./total no.§	ml			
Trial fluid								
Day 1¶	374/397	1500	1000–1500	375/400	1500	1000–2000	0.09	
Day 2	288/379	1500	1000–2000	307/380	1500	950–2000	0.50	
Day 3	176/330	1000	500–1500	170/326	1000	500–1500	0.78	
Open-label trial fluid								
Day 1¶	157/397	1500	1000–2000	177/400	1500	800–2500	0.21	
Day 2	114/379	1000	500–1500	133/380	1000	500–2000	0.13	
Day 3	54/329	900	500–1000	57/326	1000	500–1250	0.69	
Other fluids								
Day -1**	356/366	3500	2000–4938	370/385	3000	2000–4868	0.08	
Day 1¶	389/394	2235	1325–3197	393/396	1976	1077–3046	0.12	
Day 2	373/376	2980	2143–3960	369/371	2905	2094–3780	0.50	
Day 3	313/316	3150	2365–3910	315/317	3035	2183–3924	0.33	
Blood products††								
Day -1**	90/392	838	480–1435	88/399	600	490–1195	0.69	
Day 1¶	109/397	590	300–1100	89/400	600	490–980	0.13	
Day 2	115/378	600	350–1100	78/379	526	300–1030	0.001	
Day 3	81/327	500	300–980	68/326	598	300–750	0.28	
Total‡‡	243/376	1340	566–2700	204/380	1055	600–2755	0.003	

\* Detailed data on other fluids, blood products, and fluid balances are given in Tables S2 and S3 in the Supplementary Appendix.

† The Wilcoxon signed-rank test was used to compare differences in fluid volume between the starch group and the Ringer's acetate group.

‡ Values are for the patients who received the intervention on the day.

§ The number of patients refers to those who received the specific solution, and the total number refers to those who had data registered. Total numbers that are smaller than the group totals reflect the exclusion of patients who died, were discharged from the ICU, or had missing data.

¶ Day 1 was from the time of randomization to the next start of the 24-hour fluid chart in the ICU; the median duration was 14 hours (interquartile range, 8 to 19).

|| Other fluids included crystalloids, nutrition, water, fluid with medications, synthetic colloids, and albumin.

\*\* Day -1 refers to the 24 hours before randomization.

†† Blood products included packed red cells, fresh-frozen plasma, and platelet concentrates.

‡‡ The values shown are cumulative data for the full trial period in the ICU, to a maximum of 90 days after randomization.

coagulation was impaired and the use of red cells increased, which may have late adverse effects.<sup>23</sup> A high fraction of HES is taken up and deposited in tissues, where it cannot be metabolized and it acts as a foreign body.<sup>24</sup> Long-term toxic effects of HES deposition have been described in the kidney, liver, and bone marrow.<sup>25–27</sup> Together, all these negative effects of HES may have caused the late deaths observed in our trial and in the VISEP trial.

Colloids are generally considered to be more potent plasma volume expanders than crystalloids. The natural colloid albumin is likely to have a plasma volume-expanding potency that is 40 percent higher than that of saline,<sup>28</sup> but the pharmacokinetics of HES 130/0.42 are different from those of albumin.<sup>24</sup> In this large trial of masked fluid resuscitation with HES 130/0.42 as compared with Ringer's acetate, we did not observe significant

**Table 3.** Primary and Secondary Outcomes.\*

Outcome	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)	Relative Risk (95% CI)	P Value
<b>Primary outcome</b>				
Dead or dependent on dialysis at day 90 — no. (%)	202 (51)	173 (43)	1.17 (1.01–1.36)	0.03
Dead at day 90 — no. (%)	201 (51)	172 (43)	1.17 (1.01–1.36)	0.03
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
<b>Secondary outcome measures</b>				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic reaction — no. (%)†	1 (0.25)	0	—	0.32
SOFA score at day 5 — median (interquartile range)	6 (2–11)	6 (0–10)	—	0.64
Use of renal-replacement therapy — no. (%)‡	87 (22)	65 (16)	1.35 (1.01–1.80)	0.04
Use of renal-replacement therapy or renal SOFA score $\geq 3$ — no. (%)§	129 (32)	108 (27)	1.20 (0.97–1.48)	0.10
Doubling of plasma creatinine level — no. (%)†	148 (41)	127 (35)	1.18 (0.98–1.43)	0.08
Acidosis — no. (%)¶	307 (77)	312 (78)	0.99 (0.92–1.06)	0.72
Alive without renal-replacement therapy — mean % of days	91	93	—	0.048
Use of mechanical ventilation — no. (%)†	325 (82)	321 (80)	1.02 (0.95–1.09)	0.61
Alive without mechanical ventilation — mean % of days	62	65	—	0.28
Alive and out of hospital — mean % of days	29	34	—	0.048

\* For severe bleeding and severe allergic reaction, data were missing for 1 patient in the Ringer's acetate group. For doubling of the plasma creatinine level, data were missing for 38 patients in the HES 130/0.42 group and 34 patients in the Ringer's acetate group. For alive without mechanical ventilation, data were missing for 1 patient in the Ringer's acetate group. CI denotes confidence interval.

† Outcomes are for patients in the ICU during the 90-day trial period.

‡ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period.

§ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period or with a renal SOFA score of 3 or higher after the patient had a renal SOFA score of 2 or lower at randomization.

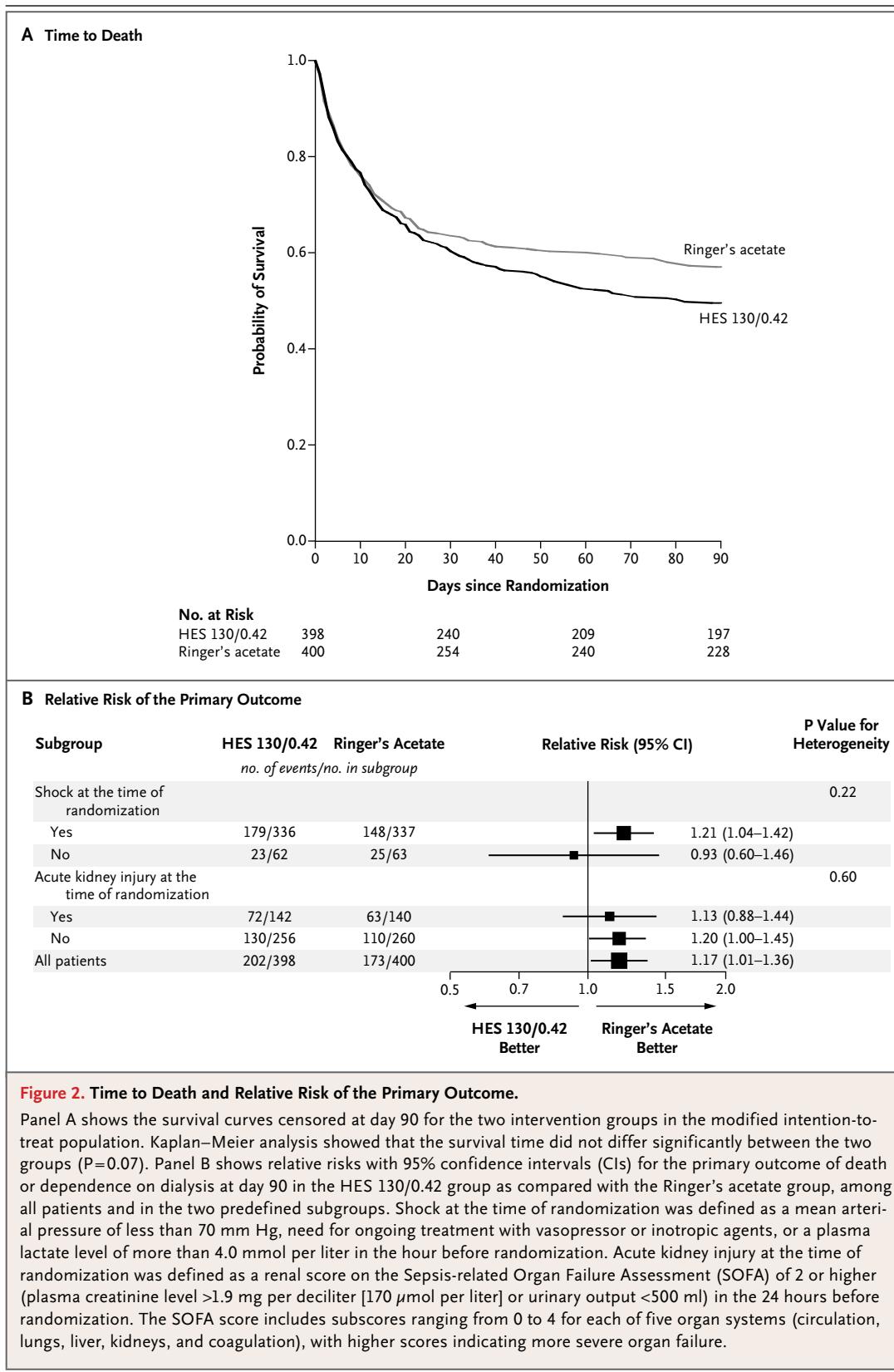
¶ Acidosis was defined as an arterial pH of less than 7.35.

|| The mean percentage of days was calculated as the number of days without renal-replacement therapy or mechanical ventilation or the number of days out of the hospital divided by the number of days alive in the 90-day follow-up period.

differences in trial-fluid volumes between the study groups, a finding that is in line with the results of a smaller trial that compared HES 130/0.4 (Voluven) with 0.9% saline in patients with sepsis.<sup>29</sup> This finding and the fact that none of the other fluid volumes or balances differed markedly between the groups raises the question of whether there actually is a difference in potency between HES 130/0.42 and crystalloids in patients with severe sepsis.

The strengths of our trial include a low risk of bias, because group assignments were concealed and all trial procedures were blinded. It is reasonable to assume that our results are generalizable, because patients were recruited in univer-

sity and nonuniversity hospitals with the use of broad inclusion criteria and few exclusion criteria; the majority of screened patients were included. The trial protocol was pragmatic, with routine practice maintained except for fluid resuscitation. In addition, most of the characteristics of the patients were similar to those of ICU patients with sepsis in other trials.<sup>4,30,31</sup> We included more patients who were in shock or mechanically ventilated than have other trials of fluid resuscitation in ICU patients with severe sepsis.<sup>4,31</sup> Outcome rates in our trial were similar to those in previous trials with respect to severe bleeding,<sup>14</sup> use of renal-replacement therapy,<sup>4,31</sup> and mortality.<sup>4,31</sup>



Our trial has certain limitations. The pragmatic trial design did not include hemodynamic monitoring or cointerventions in the protocol except for recommendations to ask centers to follow international guidelines.<sup>2</sup> Whether this affected the results cannot be assessed. We did not assess all cointerventions during the trial period. Because the trial was large, was blinded, and used stratified randomization, it is less likely that any imbalance in concomitant interventions affected the results. We included patients with acute kidney injury at the time of randomization. Their inclusion is unlikely to have affected the trial results, because acute kidney injury occurred with equal frequency in the two intervention groups and because the effect of HES 130/0.42 did not differ significantly between patients with and those without acute kidney injury at the time of randomization. Seventy-seven patients were given open-label synthetic colloids during the trial period. The use of these agents is unlikely to have affected the results, because the frequency of use was similar in the two intervention groups and because the per-protocol analyses, from which these patients were excluded, supported the primary analysis. Such protocol violations are difficult to prevent in multicenter trials in the ICU, and similar frequen-

cies were observed in the two other large trials of fluid therapy in ICU patients.<sup>4,28</sup> Sixty-nine patients were given trial fluid at doses higher than the maximum daily dose. To limit the potential harm to trial participants from high volumes of HES, we defined the dosage a priori to be lower than that recommended by the manufacturers of HES and used ideal body weight in the dosage calculations. Therefore, only two patients in our trial received HES 130/0.42 at a dose higher than the maximum daily dose recommended by the manufacturers.

In conclusion, patients with severe sepsis who received fluid resuscitation with HES 130/0.42, as compared with those who received Ringer's acetate, had a higher risk of death at 90 days, were more likely to receive renal-replacement therapy, and had fewer days alive without renal-replacement therapy and fewer days alive out of the hospital.

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#### APPENDIX

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