Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Trial fluid composition
6% hydroxyethyl starch (HES) with a molecular weight of 130 kDa and a substitution ratio of 0.42 (6% Tetraspan®, B. Braun Medical AG, Melsungen, Germany). One liter contains HES 130/0.42 60 g, Na+ 140.0 mmol, K^+ 4.0 mmol, Ca^{++} 2.5 mmol, Mg^{++} 1.0 mmol, Cl^- 118.0 mmol, malic acid 5.0 mmol and acetate 24.0 mmol.

Ringer's acetate (Sterofundin ISO®, B. Braun). One liter contains Na+ 145.0 mmol, K^+ 4.0 mmol, Ca^{++} 2.5 mmol, Mg^{++} 1.0 mmol, Cl^- 127.0 mmol, malic acid 5.0 mmol and acetate 24.0 mmol.

Trial definition of fluid resuscitation
Fluid resuscitation was a bolus of intravenous fluid, which was given to increase intravascular volume. The resuscitation fluid should be given in addition to that required to replace ongoing insensible losses, urinary losses etc. or for nutrition.

Trial criteria for severe sepsis
Sepsis was defined as a (1) DEFINED FOCUS OF INFECTION AND (2) at least TWO systemic inflammatory response syndrome (SIRS) criteria.[1]

(1) DEFINED FOCUS OF INFECTION was indicated by either

(i) An organism grown in blood or sterile site

OR

(ii) An abscess or infected tissue (e.g. pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc).

(2) The 4 SIRS criteria were:

1. CORE TEMPERATURE > 38°C or < 36°C. (Core temperature was rectal, urinary bladder, central line, or tympanic). If oral, inguinal or axillary temperatures were used, 0.5°C was added to the measured value. Hypothermia < 36°C was confirmed by core temperature only. We used the most deranged value recorded in the 24 hours before randomization.
2. HEART RATE > 90 beats/minute. If the patient had atrial arrhythmia, the ventricular rate was recorded. If the patients had known medical condition or were receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they had to meet two of the remaining three SIRS criteria. We used the most deranged value recorded in the 24 hours before randomization.
3. RESPIRATORY RATE > 20 breaths/minute, $PaCO_2$ < 32 mmHg (4.3 kPa) or mechanical ventilation for an acute process. We used the most deranged respiratory rate or $PaCO_2$ recorded in the 24 hours before randomization.
4. WHITE BLOOD CELL COUNT of >12 x 10^9/liter or < 4 x 10^9/liter or > 10% immature neutrophils (band forms). We used the most deranged value recorded in the 24 hours before randomization.

Severe sepsis was defined as SEPSIS plus at least ONE ORGAN FAILURE, except when that organ failure was already present 48 hours before the onset of sepsis.

ORGAN FAILURE was defined as a Sepsis-related Organ Failure Assessment (SOFA) score > 2 for the organ in question (Table S9).[2]

Calculation of the maximum daily dose of trial fluid
The following was calculated electronically for each individual patient in the web-based screening form (Expertmaker, Malmö, Sweden) to reduce the risk of giving too high doses of trial fluid:

- The maximum daily dose of trial fluid was based on estimated ideal body weight (men: estimated height in cm – 100; women: estimated height in cm – 105).
- The calculated maximum daily dose of trial fluid (ideal body weight in kg x 33 ml/kg) was reduced to the nearest 500 ml.
- On the 1st day of the trial, any volume of synthetic colloids given in the 24 hours prior to randomization was subtracted from the calculated maximum daily dose of trial fluid allowed.

Protocol violations
Sixty-nine patients (9%) received trial fluid above the protocolized daily maximum dose (median volume 500 (interquartile range 500-1000) ml), 28 in the HES 130/0.42 group and 41 in the Ringer's acetate group. This occurred mainly on the first trial day (n=45). Only two patients in the HES 130/0.42 group received more than the recommended daily dose by the manufacturers of 50 ml/kg and this occurred on single days only.

Seventy-seven patients received open-label synthetic colloids (67 HES 130/0.42 and 10 dextran 70) in the ICU in the 90-day trial period, 39 in the HES 130/0.42 group and 38 in the Ringer's acetate group.

In 28 cases consent was either not granted or withdrawn by the next of kin or the patient, 17 in the HES 130/0.42 group and 11 in the Ringer's acetate group. This occurred 35 (14-72) hours after randomization during which the patients received 1813 (1000-2500) ml of trial fluid. Continued data registration and use of data was allowed in all these cases.

Trial populations
Intention-to-treat population: All randomized patients. This population was not analyzed in the 6S-trial.

Modified intention-to-treat population: All randomized patients except those who

- Withdrew consent for the use of data

OR

- Were not eligible for randomization according to the inclusion/exclusion criteria AND never had the intervention (masked trial fluid)

Per-protocol populations
Two per-protocol analyses were planned to allow the first analysis to be done before the unblinding of the data. The second per-protocol analysis was done after unblinding the data. In contrast to the first analysis the patients in the HES 130/0.42 group who had received open-label synthetic colloid after randomization were included in the second per-protocol analysis.

Per-protocol population no. 1:
All randomized patients except patients having one or more major protocol violations defined as

- Patients who were not eligible for randomization according to the inclusion/exclusion criteria.

OR

- Patients who never had the intervention (masked trial fluid).

OR

- Patients who accidentally received wrong intervention (intervention error).

OR

- Patients who received any synthetic colloid after randomization.

OR

- Patients who were withdrawn from the protocol because the proxy, the relatives, the general practitioner or the patient himself withdrew consent.

Per-protocol population no. 2:
All randomized patients except patients having one or more major protocol violations defined as
- Patients who were not eligible for randomization according to the inclusion/exclusion criteria.

OR
- Patients who never had the intervention (masked trial fluid).

OR
- Patients who accidentally received wrong intervention (intervention error).

OR
- Patients in the Ringer's acetate arm, who received any synthetic colloid after randomization.

OR
- Patients who were withdrawn from the protocol because the proxy, the relatives, the general practitioner or the patient himself withdrew consent.

Per-protocol analyses
Results of per-protocol analysis no. 1
The per-protocol no. 1 analysis of the primary outcome showed that 673 patients (335 from the HES 130/0.42 group and 338 from the Ringer's acetate group) could be included in this analysis. The primary outcome occurred in 165 (49%) of the patients in the HES 130/0.42 group and in 146 (43%) in the Ringer's acetate group exhibiting an intervention effect of an absolute risk difference of 6% or a relative risk of 1.14 (95% confidence limits: 0.97-1.34, P=0.12)

Results of per-protocol analysis no. 2
The per-protocol no. 2 analysis of the primary outcome showed that 705 patients (367 from the HES 130/0.42 group and 338 from the Ringer's acetate group) could be included in this analysis. The primary outcome occurred in 184 (50%) of the patients in the HES 130/0.42 group and in 146 (43%) in the Ringer's acetate group exhibiting an intervention effect of an absolute risk difference of 7% or a relative risk of 1.16 (95% confidence limits: 0.97-1.37, P=0.07)

Handling of missing data

Logical imputations performed for baseline variables

SAPS II in the 24 hours prior to randomization
The score is based on 17 components each measured in the first 24 hours in the ICU. In the baseline form, we registered values measured before randomization only. Randomization immediately after ICU-admittance therefore resulted in missing values. However, day 1 values measured shortly afterwards may reflect the patient's condition.

Since day 1 ran from randomization until the start of the next "fluid day" of the ward, day 1 had a short duration in some patients. In these situations there were missing data both at baseline and on day 1. However, data from day 2 may reflect the patient's condition in these situations.

Missing PaO_2/FiO_2-ratio: If the patient was randomized within 24 hours after ICU-admittance, values from day 1 were used for SAPS-scoring.

Missing diuresis: If the patient was randomized within 24 hours after ICU-admittance AND creatinine < 100 µmol/liter (1.2 mg/deciliter) AND diuresis on day 1 > 1000 ml, the patient's kidney function was considered normal and the patient was given zero points.

Missing leucocytes: If the leucocytes were reported in the normal range in the screening form zero points were given.

Missing bilirubin: The value from day 1 was used. If this value was also missing zero points were given, if the doctor had reported normal bilirubin in the screening form.

The above imputations reduced the number of incomplete SAPS II values from 296 to 213.

For the remaining 213 patients 'best' and 'worst' scores were calculated covering all possible true scenarios. Setting missing SAPS-components to zero points made the 'best' possible score.

Patients were given the highest obtainable points for the calculation of the 'worst' possible score. However, for Glasgow Coma Scale (GCS) and blood pressure the imputation depended on other data as well:

If GCS score was < 13 in the screening form, 26 points were imputed, otherwise only 5 points were imputed.

If the lowest mean arterial pressure at baseline was >70 mmHg, then the systolic blood pressure must also have been > 70 mmHg and 5 points were imputed instead of 13 points.

SOFA score in the 24 hours prior to randomization
This score does not depend on when the patient was admitted to the ICU.

Missing renal component: No missing values.

Missing platelet count: Values from day 1 were used; otherwise from day 2.

Missing plasma bilirubin: Values from day 1 were used; otherwise from day 2. If still missing, the patient got zero points if the doctor had reported normal bilirubin in the screening form.

Missing PaO_2/FiO_2-ratio: Values from day 1 were used.

Missing cardiovascular component: One missing value. According to the screening form the patient had normal blood pressure and did not receive any vasopressors or inotropes. This patient was given 0 points.

The above imputations reduced the number of incomplete SOFA scores from 121 to 2.

Missing outcome data
For the primary outcome measure and most of the secondary outcomes we had full data sets on all 798 patients.

There were missing data for the following secondary outcome measures:

Doubling of plasma creatinine because 62 patients had no pre-admission plasma creatinine (33 and 29 patients in the HES 130/0.42 and Ringer's acetate groups, respectively), 9 patients died early and had no creatinine measured after randomization and one patient had source data missing for five ICU days (Ringer's acetate group). We did a complete case analysis of this outcome (726 patients).

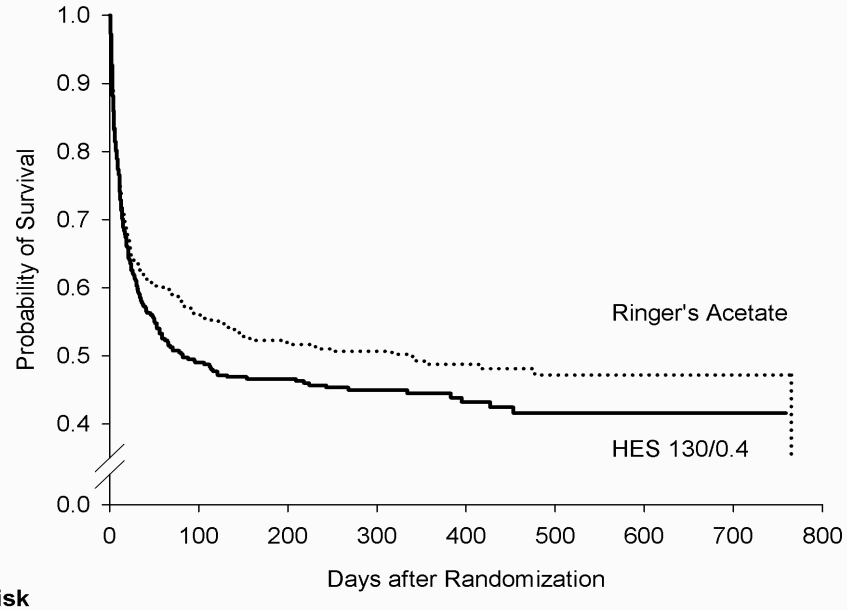
Severe bleeding because one patient had source data missing for five ICU days (Ringer's acetate group). We did a complete case analysis of this outcome (797 patients).

Severe allergic reaction because one patient had source data missing for five ICU days (Ringer's acetate group). We did a complete case analysis of this outcome (797 patients).

Days alive without mechanical ventilation because one patient had source data missing for five ICU days (Ringer's acetate group). We did a complete case analysis of this outcome (797 patients).

Abstract written before breaking the randomization code
BACKGROUND
Hydroxyethyl starch (HES) 130/0.4 is widely used for fluid resuscitation in intensive care units (ICU), but largely unstudied 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 using either 6% HES 130/0.4 or Ringer's acetate up to 33 milliliter/kg/day. The primary outcome measure was either death or end-stage kidney failure 90 days after randomization and secondary outcomes included acute kidney failure, need of dialysis and severe bleeding.
RESULTS
Of the 804 randomized patients, 798 were included in the modified intention-to-treat population. The two intervention groups had comparable baseline characteristics. At 90 days after randomization, 202 of the 398 patients (51%) assigned to 0 fulfilled the primary outcome of death or end-stage kidney failure compared with 173 of the 400 patients (43%) assigned to 1, relative risk 1.17 (95% confidence interval 1.01 – 1.36; P=0.034). Also 90-day mortality and need of dialysis was higher and days alive without dialysis and days alive and out of hospital was lower in the patients in the 0 group compared with those in the 1 group. The results were confirmed in multivariate analyses adjusting for known risk factor at baseline and in per protocol analyses.
CONCLUSIONS
Patients with severe sepsis who were fluid resuscitated with 0 had higher 90-day mortality and need of dialysis and fewer days alive without dialysis and out of hospital compared with those receiving 1.

Figure S1. Time to Death Analysis
Shown are the survival curves censored at latest follow-up on February 16th 2012 for the two intervention groups in the modified intention-to-treat population. Kaplan Meier analysis showed that the survival time did not differ significantly between the groups (P=0.14).



No. at Risk								
HES 130/0.4	398	193	152	104	67	34	12	5
Ringer's Acetate	400	224	169	125	81	46	19	9

Table S1. More Baseline Characteristics

	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)
Actual body weight – kg	77 (65-89)	76 (65-86)
Diabetes mellitus – no. (%)	52 (13)	57 (14)
Arterial hypertension – no. (%)	156 (39)	156 (39)
Previous admission for – no. (%)		
Heart failure or myocardial infarction	49 (12)	62 (16)
Stroke	31 (8)	42 (11)
Asthma or COPD	60 (15)	58 (15)
Pre-admission plasma creatinine > 100 µmol/liter (1.2 mg/deciliter) – no. (%)	57 (14)	64 (16)
Hematological malignancy – no. (%)	36 (9)	36 (9)
Positive culture from blood or a sterile site – no. (%)	81 (20)	82 (21)
Time from ICU admission to randomization – hours	3.7 (1.3-12.9)	4.0 (1.4-12.6)
Organ failures *		
Cerebral failure †	135 (34)	121 (30)
Respiratory failure	289 (73)	293 (73)
Circulatory failure	259 (65)	252 (63)
Hepatic failure	47 (12)	44 (11)
Kidney injury	142 (36)	140 (35)
Coagulation failure	81 (20)	74 (19)
Use of potential nephrotoxic agents §	118 (30)	120 (30)
Use of synthetic colloids – no. (%) ¶	169 (42)	168 (42)
Volume of synthetic colloids – ml ¶	700 (500-1000)	500 (500-1000)

Values with ranges are medians (interquartile ranges).
COPD denotes chronic obstructive pulmonary disease, HES hydroxyethyl starch, ICU intensive care unit.
*Defined as Sepsis-related Organ Failure Assessment score of 2 or above in the given organ system at randomization (Table S9).[2] Most patients had two or more failing organ systems.
† Glasgow Coma Scale (GCS) score < 13 without a structural cause. If the patient was sedated, the GCS score estimated before sedation was used.
§ Any of the following agents given during hospital admission but prior to randomization: IV gentamicin, IV vancomycin, IV amphotericin B, IV polymyxins, IV dye contrast, ciclosporin A, non-steroid anti-inflammatory drugs, ganciclovir, tacrolimus, ifosfamid, atripla, or candesartancilexetil.
¶ Hydroxyethyl starch, gelatin, or dextran given in the 24 hours prior to randomization. Volumes given are medians (interquartile ranges) for those receiving colloids.

Table S2. Details on Fluid Therapy, Blood Products, and Nutrition

Variable	HES 130/0.42 (N=398)		Ringer's Acetate (N=400)		P Value
	No. receiving / No. at risk †	Value	No. receiving / No. at risk †	Value	
Albumin (ml)					
Day -1 ¶	36/391	500 (250-625)	38/397	275 (250-750)	0.87
Day 1 ‡	15/397	250 (200-500)	14/399	250 (200-300)	0.85
Day 2	15/379	300 (200-500)	12/380	325 (150-700)	0.56
Day 3	15/328	200 (100-500)	14/326	200 (100-300)	0.86
Total §	80/379	500 (225-1200)	65/381	400 (250-1000)	0.14
Crystalloids (ml)					
Day -1 ¶	350/373	2500 (1400-4000)	349/386	2400 (1400-4000)	0.20
Day 1 ‡	235/397	1000 (525-2000)	223/399	1000 (500-2000)	0.22
Day 2	162/378	740 (250-1397)	136/379	1000 (500-1510)	0.15
Day 3	125/322	800 (200-1060)	101/323	850 (400-1500)	0.10
Total §	310/363	2500 (1000-6000)	290/358	2300 (1000-4970)	0.05
Packed red blood cells (ml)					
Day -1 ¶	71/392	550 (300-1045)	65/399	500 (300-900)	0.50
Day 1 ‡	84/397	490 (279-600)	59/400	490 (275-840)	0.03
Day 2	82/378	490 (250-600)	54/379	300 (245-510)	0.005
Day 3	53/328	300 (245-500)	43/326	490 (250-600)	0.35
Total §	220/377	900 (490-1715)	173/380	900 (551-1715)	0.005
Fresh frozen plasma (ml)					
Day -1 ¶	42/392	600 (540-1113)	38/399	600 (540-1080)	0.57
Day 1 ‡	44/397	600 (540-800)	41/400	600 (540-1080)	0.76
Day 2	47/378	700 (540-1080)	30/380	560 (540-813)	0.03
Day 3	28/328	540 (526-950)	18/326	585 (528-1080)	0.14
Total §	113/377	1080 (540-1815)	96/382	950 (540-2165)	0.14
Platelets (ml)					
Day -1 ¶	25/392	600 (350-700)	22/399	480 (350-1050)	0.62
Day 1 ‡	22/397	350 (300-600)	21/400	350 (350-700)	0.88
Day 2	31/378	400 (350-700)	22/380	700 (350-710)	0.21
Day 3	24/327	675 (350-735)	27/326	600 (350-700)	0.69
Total §	71/376	700 (350-2100)	53/382	1000 (650-3500)	0.09
Nutrition (ml) **					
Day 1 ‡	242/396	638 (315-1102)	248/399	632 (300-1089)	0.77
Day 2	321/378	1250 (870-1622)	321/378	1192 (775-1600)	0.46

Day 3	296/321	1490 (1000-1855)	294/321	1478 (947-1785)	0.34
Total §	308/350	8609 (3125-19256)	299/346	7666 (2500-19194)	0.34

Values are medians (interquartile ranges) of those patients who did receive the intervention on that day(s). HES denotes hydroxyethyl starch.
† No. receiving is those patients who did receive the specific solution on the given day(s). No. at risk is those patients who had data registered. Where the no. is below the no. allocated to the group this is due to death, ICU discharge or missing source data.
¶ In the 24 hours prior to randomization.
‡ The first day was from the time of randomization to the next start of the specific ICU's 24-hour fluid chart and lasted median 14 (8-19) hours.
§ Cumulative data for the full trial period in the ICU to a maximum of 90 days after randomization.
** Added volumes of enteral and parenteral nutrition including any glucose solution > 9% and any protein or lipid solutions.

Table S3. Urinary Outputs and Fluid Balances

Variable	HES 130/0.42 (N=398)		Ringer's Acetate (N=400)		P Value
	No. with data / No. at risk †	Value	No. with data / No. at risk †	Value	
Urine output (ml)					
Day 1 ‡	394/398	1938 (1000-2860)	396/400	1800 (920-2820)	0.31
Day 2	377/380	2150 (1195-2950)	374/382	2348 (1395-3300)	0.03
Day 3	321/331	2400 (1430-3300)	321/327	2550 (1595-3500)	0.17
Total §	333/398	14890 (5340-32480)	331/400	13700 (5720-32550)	0.69
Fluid balance (ml)					
Day 1 ‡	387/398	2206 (941-3895)	391/400	2200 (919-3798)	0.92
Day 2	372/380	1828 (625-3355)	367/382	1656 (510-3043)	0.13
Day 3	310/331	975 (1-2145)	314/327	765 (-90-1964)	0.31
Total §	288/398	5452 (1876-10518)	291/400	4616 (1271-9530)	0.17

Values are medians (interquartile ranges) of those patients who had data registered on that day(s).
HES denotes hydroxyethyl starch.
† No. with data is those patients where data were registered for that day(s). No. at risk is those patients who were in the ICU on that day(s). Where the no. is below the no. allocated to the group this is due to death or ICU discharge.
‡ The first day was from the time of randomization to the next start of the specific ICU's 24-hour fluid chart and lasted median 14 (8-19) hours.
§ Cumulative data for the full trial period in the ICU to a maximum of 90 days after randomization.

Table S4. Circulatory Parameters at Baseline and in the First 24 Hours after Randomization

Variable	HES 130/0.42 (N=398)		Ringer's Acetate (N=400)		P Value
	No. assessed †	Value	No. assessed †	Value	
CVP – mm Hg					
Baseline	110	10 (7-13)	101	10 (8-13)	0.26
0 – 12 hours ‡	151	11 (7-14)	146	10 (7-13)	0.37
12 – 24 hours ‡	129	11 (6-14)	125	10 (6-13)	0.16
$ScvO_2$ – %					
Baseline	175	75 (67-83)	152	73 (65-82)	0.13
0 – 12 hours ‡	181	72 (66-77)	193	73 (65-78)	0.84
12 – 24 hours ‡	131	75 (68-79)	133	73 (67-79)	0.48
Lactate – mmol/liter					
Baseline	385	2.0 (1.3-3.5)	387	2.1 (1.4-3.7)	0.34
0 – 12 hours ‡	390	2.2 (1.4-3.9)	393	2.2 (1.5-3.6)	0.84
12 – 24 hours ‡	337	2.0 (1.3-3.3)	338	2.0 (1.4-2.8)	0.40

*Values are medians (interquartile ranges)
CVP denotes central venous pressure, HES hydroxyethyl starch, $ScvO_2$ central venous oxygen saturation.
† Number of patients where the measurements were documented in source data.
‡ Hours after randomization. Where more measurements were documented within the time period the lowest value of CVP and $ScvO_2$ and the highest value of lactate were registered

Table S5. Use of Potential Nephrotoxic Agents in the ICU after Randomization

	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)
IV gentamicin	14 (4)	25 (6)
IV vancomycin	78 (20)	85 (21)
IV amphotericin B	12 (3)	20 (5)
IV polymyxins	11 (3)	14 (4)
IV dye contrast	73 (18)	66 (17)
Ciclosporin A	2 (1)	5 (1)
NSAIDs	10 (3)	9 (2)
Others †	12 (3)	11 (3)

Values are number of patients (%)
HES denotes hydroxyethyl starch IV denotes intravenous, NSAIDs non-steroid anti-inflammatory drugs.
† Others include tacrolimus, voriconazole, anidulafungin, foscarnet and candesartancilexetil.

Table S6. Results of the Adjusted Analyses

	Best case scenario			Worst case scenario		
Quantity	OR	95% CI	P value	OR	95% CI	P value
Intervention (reference: no HES)	1.53	1.13 – 2.07	0.005	1.35	1.00 – 1.81	0.05
Age/year	1.03	1.02 – 1.05	<0.001	1.03	1.02 – 1.04	<0.0001
Inclusion at a university hospital (reference: not)	0.82	0.60 – 1.11	0.20	0.80	0.59 – 1.09	0.16
Diabetes (reference: not)	0.53	0.34 – 0.83	0.005	0.53	0.34 – 0.83	0.005
Hematological malignancy (reference: not)	1.79	1.02 – 3.13	0.04	1.83	1.05 – 3.19	0.03
Shock (reference: not)	1.14	0.74 – 1.76	0.54	1.20	0.78 – 1.84	0.41
Pre-admission renal dysfunction (reference: not)	1.51	0.99 – 2.31	0.06	1.58	1.04 – 2.42	0.03
Use of nephrotoxic drugs (reference: no drugs)	0.83	0.60 – 1.16	0.28	0.85	0.61 – 1.17	0.32
SOFA score excluding GCS score > 7	1.38	1.00 – 1.90	0.05	1.31	0.94 – 1.81	0.11
SAPS II > 50	1.81	1.31– 2.51	<0.001	1.94	1.140– 2.68	<0.0001

CI denotes confidence intervals, GCS Glasgow Coma Scale, HES hydroxyethyl starch, OR odds ratios, SAPS Simplified Acute Physiology Score, SOFA Sepsis-related Organ Failure Assessment.
Odds ratios and 95% confidence intervals for the intervention with HES forcing adjusting co-variates at baseline into the multivariate analysis of the primary outcome of death and dialysis-dependency 90 days after randomization. There were missing values for SAPS II, so sensitivity analyses were performed using best- and worst case scenarios to test the results of the multiple logistic regression analyses.

Table S7. Results of Post-hoc Analyses of Kidney Injury after Randomization

Mortality data for patients with post-randomization acute kidney injury* and patients treated with renal replacement therapy divided by allocation group

The interpretations of these post-hoc analyses are difficult because of the likely interaction between the HES treatment and AKI and the possible interaction between AKI (oliguria) and trial fluid administration by clinicians.[3]

Both groups

	Total no.	No. of deaths	Mortality			Total no.	No. of deaths	Mortality
RRT	152	92	61%		AKI	237	153	65%
No RRT	646	281	44%		No AKI	560	220	39%
HES 130/0.42 group								
RRT	87	57	66%		AKI	129	85	66%
No RRT	311	144	46%		No AKI	269	116	43%
Ringer's Acetate group								
RRT	65	35	54%		AKI	108	68	63%
No RRT	335	137	41%		No AKI	291	104	36%

AKI denotes acute kidney injury, HES hydroxyethyl starch, RRT renal replacement therapy
*AKI defined as kidney SOFA score > 2 (Table S9)[2] or use of RRT.

Creatinine-based RIFLE Scoring[4]

	HES 130/0.42 (n=398)		**Ringer's Acetate (n=400)**	
	No.	%	No.	%
Normal kidney function	156	43	163	45
Risk	52	14	73	20
Injury	62	17	53	15
Failure	84	23	67	18
Loss	7	2	9	3
ESKD	1	0.3	1	0.3
	362		366	

ESKD denotes end-stage kidney disease, HES hydroxyethyl starch.
There were missing data for 70 patients: One patient had missing source data for 5 days in the ICU, nine patients died early and had no creatinine measured after randomization, and 62 patients did not have a pre-admission creatinine. However, two of these patients were treated with RRT > 28 days and thereby had Loss.

Creatinine-based RIFLE Scoring - substitution using the MDRD-equation[4]				
	HES 130/0.42 (n=398)		Ringer's Acetate (n=400)	
	No.	%	No.	%
Normal kidney function	167	42	171	43
Risk	60	15	80	20
Injury	69	18	59	15
Failure	90	23	74	19
Loss	7	2	9	2
ESKD	1	0.3	1	0.3
	394		394	

ESKD denotes end-stage kidney disease, HES hydroxyethyl starch, MDRD modification of diet in renal disease.
There were missing data for 10 patients: One patient had missing source data for 5 days in the ICU and nine patients died early and had no creatinine measured after randomization.

Doubling in p-creatinine OR Renal replacement therapy	HES 130/0.42 (N=398)		Ringer's Acetate (N=400)	
	No.	%	No.	%
Yes	175	44	147	37
No	223	56	253	63
Total	398		400	
				P Value 0.04

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Table S8. Results of Post-hoc Analyses of Bleeding after Randomization

Any Bleeding	**HES 130/0.42 (N=398)**		**Ringer's Acetate (N=400)**	
	No.	%	No.	%
Yes	93	23	60	15
No	305	77	339	85
Total	398		399	
				P Value 0.003

There were missing data for one patient in the Ringer's group, who had missing source data for 5 days in the ICU.