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# Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

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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

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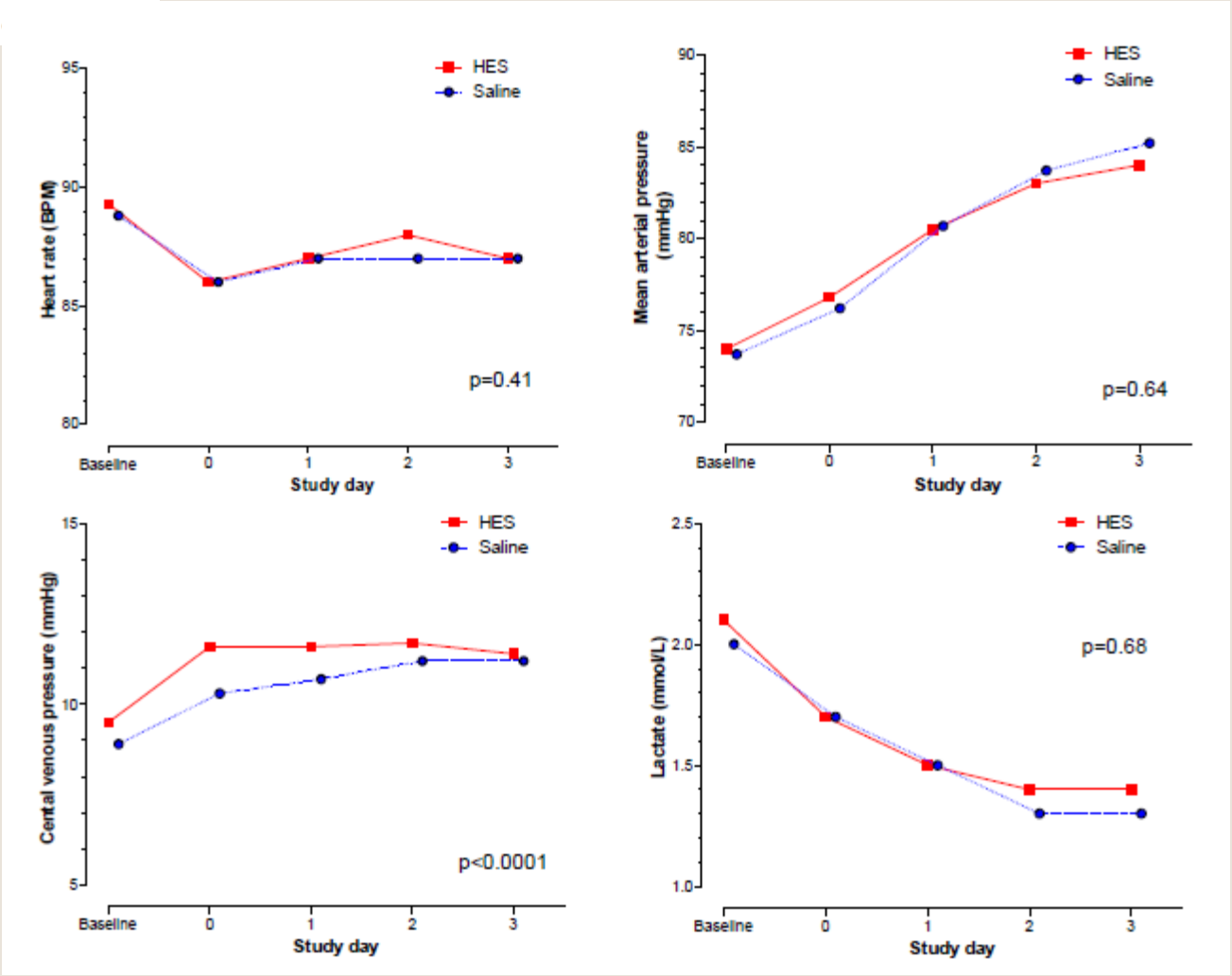

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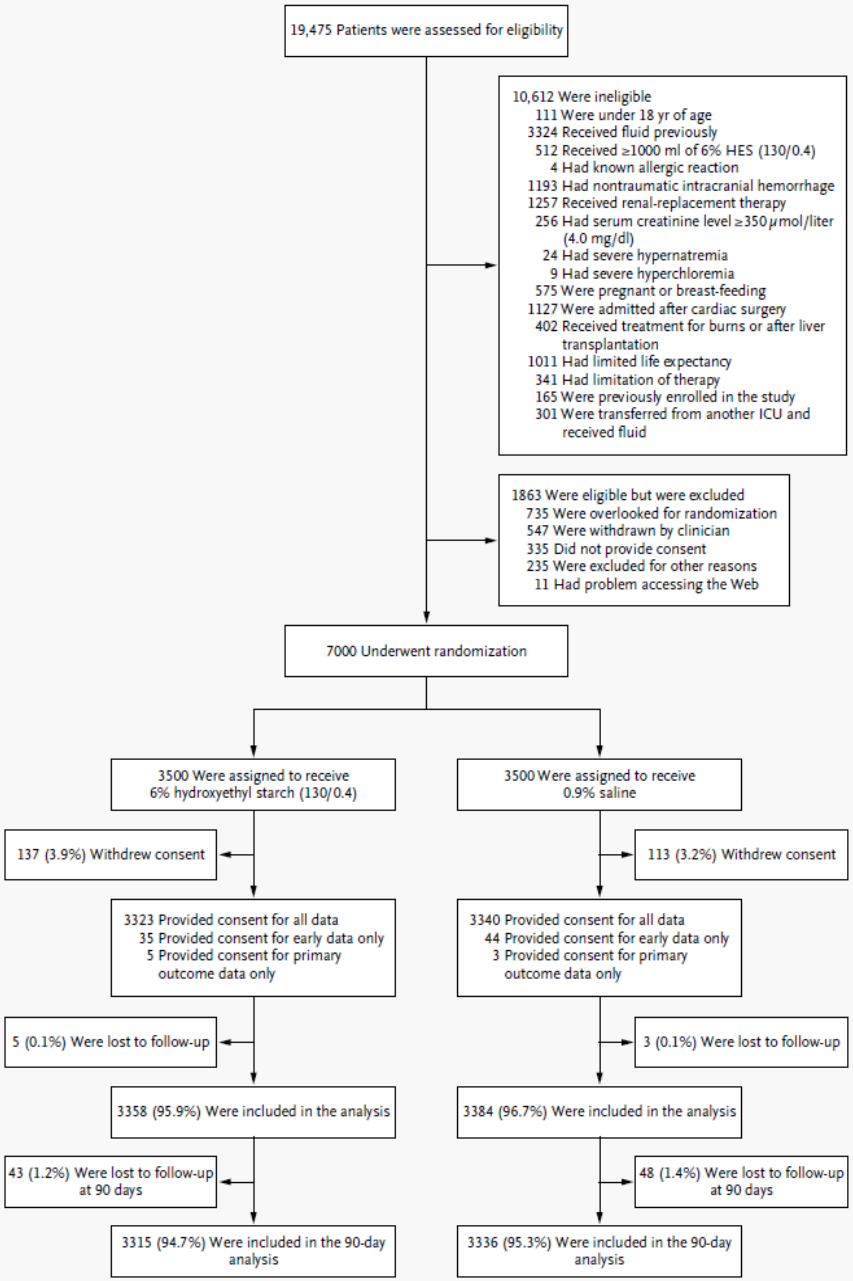


**Figure 1. Assessment, Randomization, and Follow-up of the Patients.**

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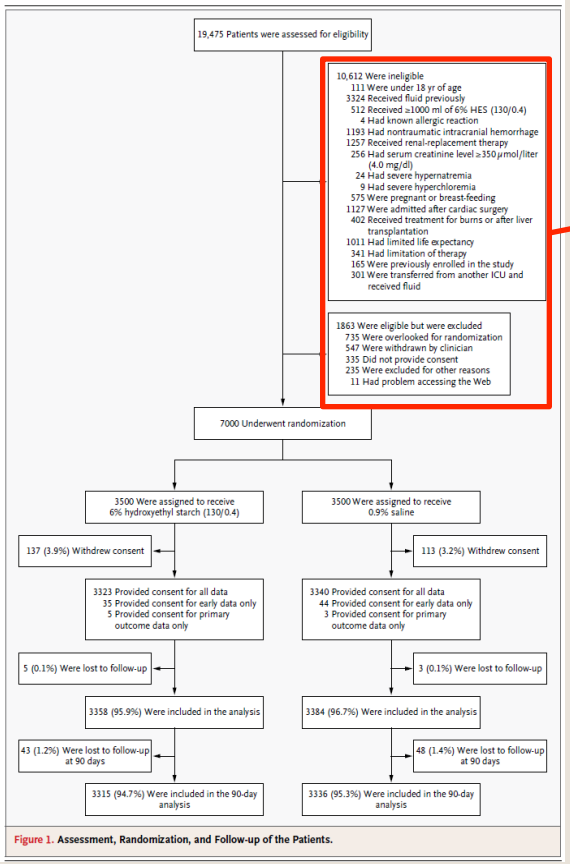


**Figure 1. Assessment, Randomization, and Follow-up of the Patients.**

10,612 Were ineligible
- 111 Were under 18 yr of age
- 3324 Received fluid previously
- 512 Received ≥1000 ml of 6% HES (130/0.4)
- 4 Had known allergic reaction
- 1193 Had nontraumatic intracranial hemorrhage
- 1257 Received renal-replacement therapy
- 256 Had serum creatinine level ≥350 μmol/liter (4.0 mg/dl)
- 24 Had severe hypernatremia
- 9 Had severe hyperchloremia
- 575 Were pregnant or breast-feeding
- 1127 Were admitted after cardiac surgery
- 402 Received treatment for burns or after liver transplantation
- 1011 Had limited life expectancy
- 341 Had limitation of therapy
- 165 Were previously enrolled in the study
- 301 Were transferred from another ICU and received fluid

1863 Were eligible but were excluded
- 735 Were overlooked for randomization
- 547 Were withdrawn by clinician
- 335 Did not provide consent
- 235 Were excluded for other reasons
- 11 Had problem accessing the Web

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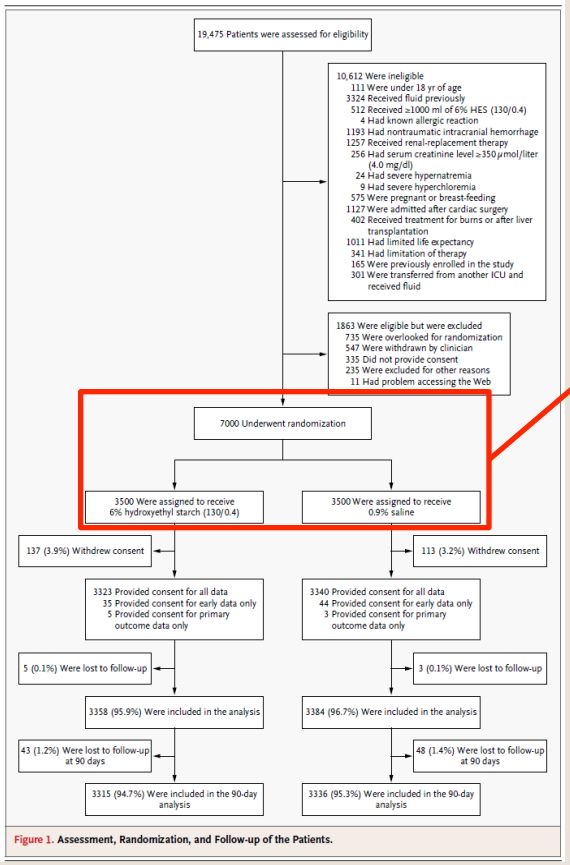
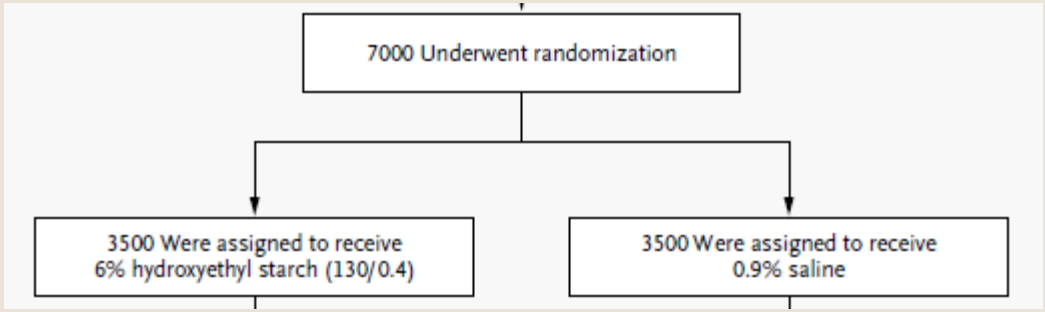



Figure 1. Assessment, Randomization, and Follow-up of the Patients.



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| Characteristic | HES (N=3358) | Saline (N=3384) |
|---|---|---|
| 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) |
| 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) |
| 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) |

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During the first 4 days, the HES group received significantly less study fluid than the saline group (mean [±SD] daily average, 526±425 ml vs. 616±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±675 ml vs. 1115±993 ml, P<0.001), resulting in a significantly lower positive net fluid balance (921±1069 ml vs. 982±1161 ml, P=0.03) (Table S4 and Fig. S1 in the Supplementary Appendix).

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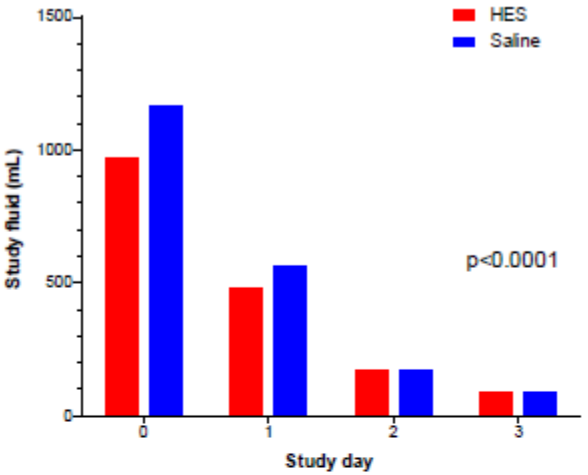


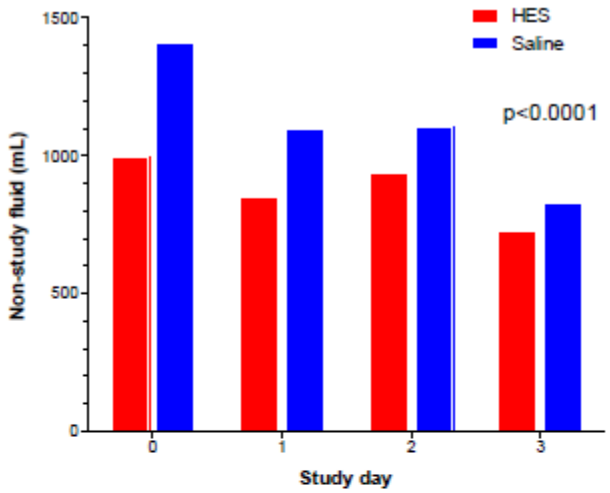


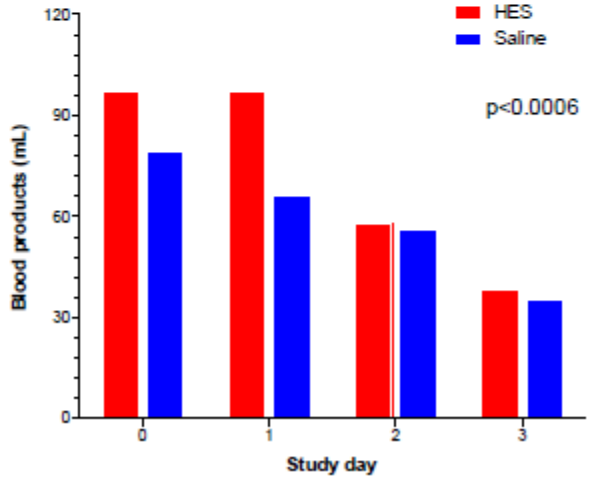


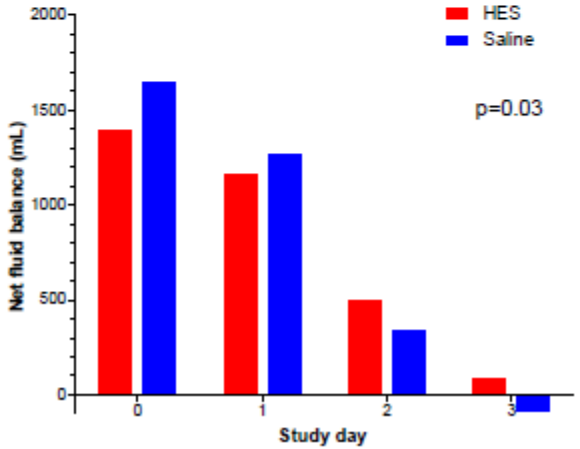

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| Variable | HES | Saline | Relative Risk (95% CI) | P Value |
|---|---|---|---|---|
| **Outcome** | | | | |
| Primary outcome of death at day 90 — no./total no. (%) | 597/3315 (18.0) | 566/3336 (17.0) | 1.06 (0.96 to 1.18) | 0.26 |
| Secondary outcomes — 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 |

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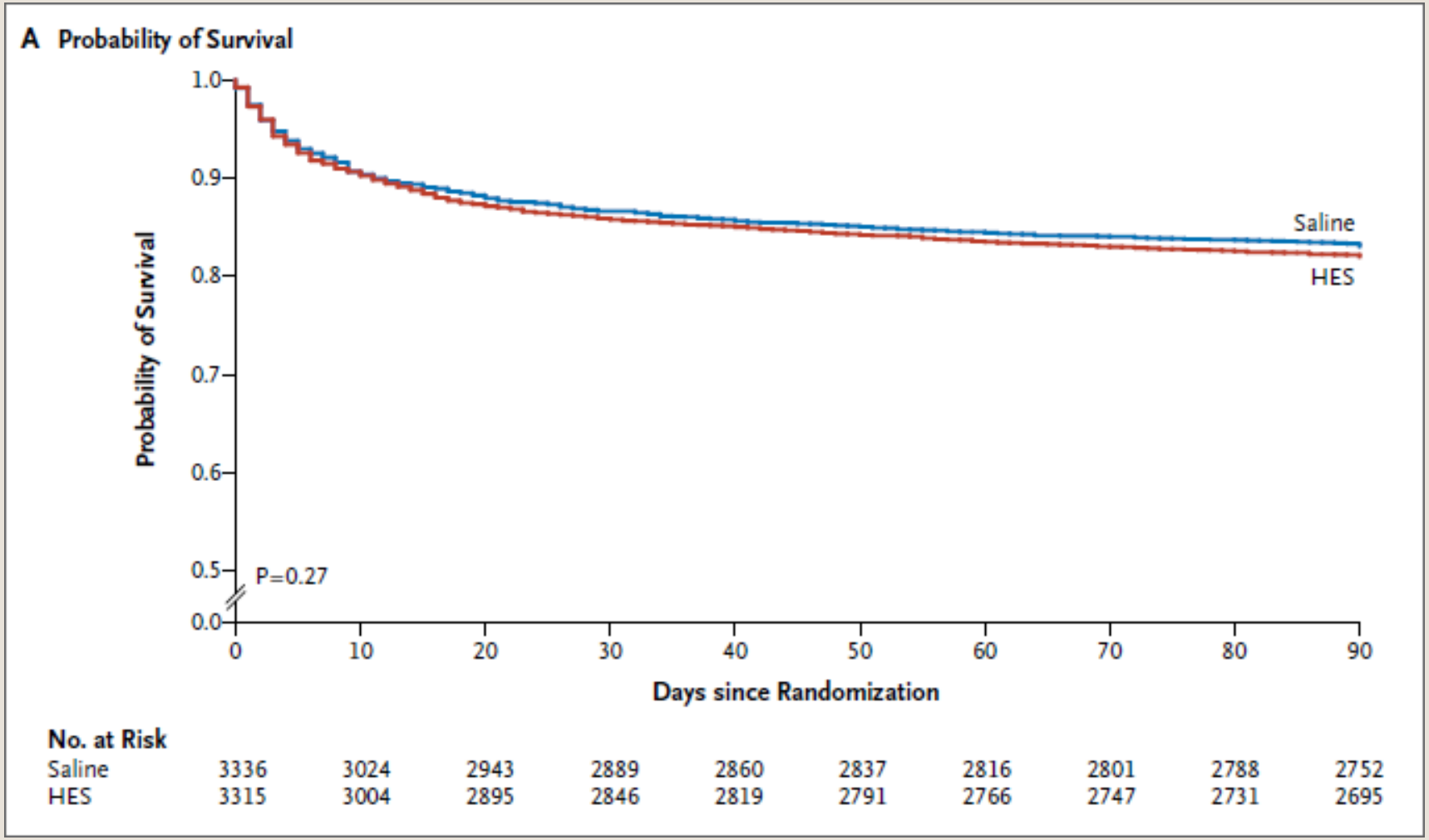

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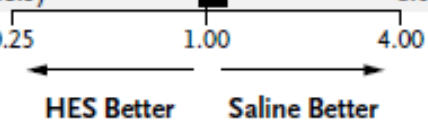
**B Subgroup Analyses**

| Subgroup | HES | Saline | Risk Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. (%)* | | | |
| Death from any cause at 90 days | 597/3315 (18.0) | 566/3336 (17.0) | 1.06 (0.96–1.18) | 0.26 |
| RIFLE criteria at randomization | | | | 0.66 |
| Presence of acute renal injury | 99/519 (19.1) | 95/503 (18.9) | 1.01 (0.78–1.30) | 0.94 |
| Absence of acute renal injury | 132/919 (14.4) | 118/896 (13.2) | 1.09 (0.87–1.37) | 0.46 |
| Sepsis at randomization | | | | 0.78 |
| Diagnosis on admission | 248/976 (25.4) | 224/945 (23.7) | 1.07 (0.92–1.25) | 0.38 |
| No diagnosis on admission | 349/2337 (14.9) | 342/2383 (14.4) | 1.04 (0.91–1.19) | 0.57 |
| Trauma | | | | 0.90 |
| Yes | 18/258 (7.0) | 18/263 (6.8) | 1.02 (0.54–1.91) | 0.95 |
| No | 579/3057 (18.9) | 548/3073 (17.8) | 1.06 (0.96–1.18) | 0.26 |
| Traumatic brain injury | | | | 0.31 |
| Yes | 1/27 (3.7) | 3/30 (10.0) | 0.37 (0.04–3.35) | 0.35 |
| No | 594/3269 (18.2) | 560/3287 (17.0) | 1.07 (0.96–1.18) | 0.23 |
| APACHE II score before randomization | | | | 0.60 |
| ≥25 | 217/590 (36.8) | 221/616 (35.9) | 1.03 (0.88–1.19) | 0.74 |
| <25 | 372/2702 (13.8) | 342/2690 (12.7) | 1.08 (0.94–1.24) | 0.25 |
| Receipt of HES before randomization | | | | 0.78 |
| Yes | 48/508 (9.4) | 42/499 (8.4) | 1.12 (0.76–1.67) | 0.57 |
| No | 547/2798 (19.5) | 522/2825 (18.5) | 1.06 (0.95–1.18) | 0.31 |



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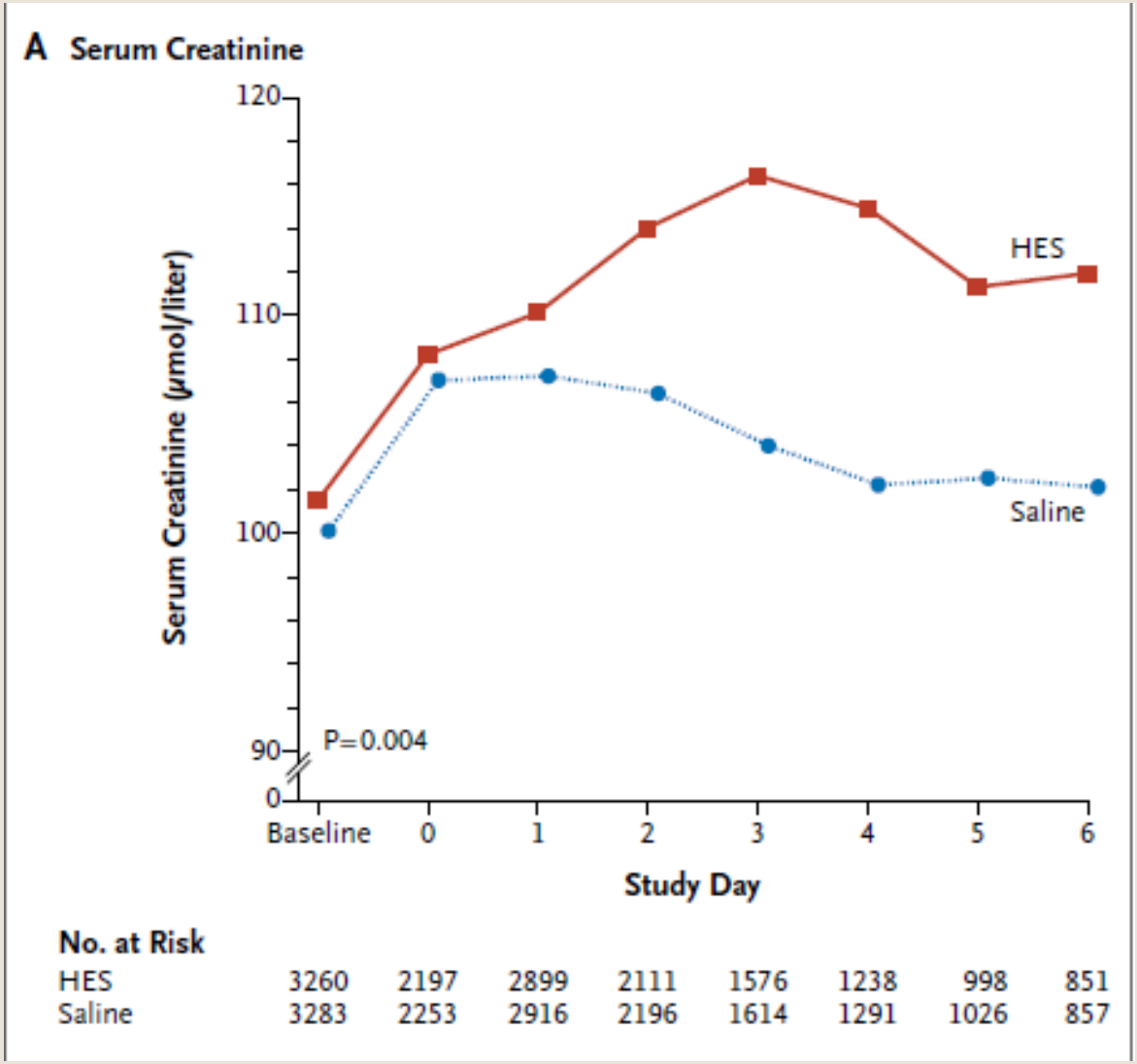

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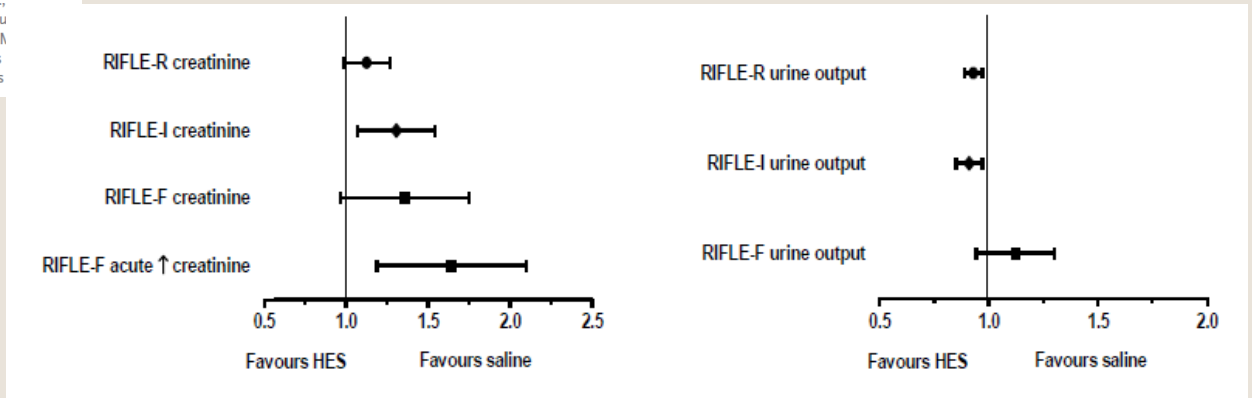


| RIFLE category and component | HES n/N (%) | Saline n/N (%) | Relative risk 95% confidence intervals | p |
|---|---|---|---|---|
| **RIFLE-R** | 1788/3309 (54.0) | 1912/3335 (57.3) | 0.94 (0.90 to 0.98) | 0.007 |
| Creatinine increase x1.5 from baseline | 462/3149 (14.7) | 415/3171 (13.1) | 1.12 (0.99 to 1.27) | 0.07 |
| Urine output<0.5 mL/kg/hr x 6 | 1701/3230 (52.7) | 1846/3266 (56.5) | 0.93 (0.89 to 0.97) | 0.002 |
| **RIFLE-I** | 1130/3265 (34.6) | 1253/3300 (38.0) | 0.91 ( 0.85 to 0.97) | 0.005 |
| Creatinine increase x2 from baseline | 245/3149 (7.8) | 191/3171 (6.0) | 1.29 (1.08 to 1.55) | 0.006 |
| Urine output<0.5 mL/kg/hr x 12 h | 1077/2977 (36.2) | 1200/3024 (39.7) | 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 |
| Creatinine increase x3 from baseline | 101/3149 (3.2) | 77/3171 (2.4) | 1.32 (0.99 to 1.77) | 0.06 |
| Creatinine ≥ 350µmol/L and ↑ ≥ 44 µmol/L in < 24h | 120/2927 (4.1) | 77/3002 (2.6) | 1.60 (1.21 to 2.12) | <0.001 |
| Urine output<0.3 mL/kg/hr x 24 h | 271/2327 (11.6) | 254/2424 (10.5) | 1.11 (0.95 to 1.31) | 0.20 |

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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.