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2 Balanced Crystalloids versus Saline in Noncritically Ill 3 Adults

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21 Abstract

22 Background

23 Comparative clinical effects of balanced crystalloids and saline are uncertain,
24 particularly in noncritically ill patients cared for outside an intensive care unit
25 (ICU).

26 Methods

27 We conducted a single-center, pragmatic, multiple-crossover trial comparing
28 balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with saline
29 among adults who were treated with intravenous crystalloids in the emergency
30 department and were subsequently hospitalized outside an ICU. The type of
31 crystalloid that was administered in the emergency department was assigned to
32 each patient on the basis of calendar month, with the entire emergency
33 department crossing over between balanced crystalloids and saline monthly
34 during the 16-month trial. The primary outcome was hospital-free days (days
35 alive after discharge before day 28). Secondary outcomes included major adverse
36 kidney events within 30 days — a composite of death from any cause, new
37 renal-replacement therapy, or persistent renal dysfunction (defined as elevation
38 of creatinine level $\geq 200\%$ of baseline) — all censored at hospital discharge or 30
39 days, whichever occurred first.

40 Results

41 A total of 13,347 patients were enrolled, with a median crystalloid volume
42 administered in the emergency department of 1079 ml and 88.3% of the patients
43 exclusively receiving the assigned crystalloid. The number of hospital-free days
44 did not differ between the balanced-crystalloids and saline groups (median, 25

1 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95%
2 confidence interval [CI], 0.92 to 1.04; P=0.41). Balanced crystalloids resulted in
3 a lower incidence of major adverse kidney events within 30 days than saline
4 (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01).

5 Conclusions

6 Among noncritically ill adults treated with intravenous fluids in the emergency
7 department, balanced crystalloids and saline resulted in no difference in the
8 number of hospital-free days. (Funded by the Vanderbilt Institute for Clinical and
9 Translational Research and others; SALT-ED ClinicalTrials.gov number,
10 NCT02614040.)

11 Administration of intravenous isotonic fluids is one of the most common medical
12 therapies, with routine use in emergency departments, hospital wards, intensive
13 care units (ICUs), and operating rooms.¹ However, it is not known whether the
14 composition of the isotonic intravenous fluid that is used has an effect on
15 patient outcomes. In the United States, saline (0.9% sodium chloride; “normal
16 saline”) is the most commonly used isotonic crystalloid, with more than 200
17 million liters administered annually.¹ The chloride concentration of saline (154
18 mmol per liter) is higher than that of human plasma (94 to 111 mmol per liter).
19 Infusion of saline generally causes hyperchloremic metabolic acidosis and may
20 increase renal inflammation and impair renal perfusion.⁴⁻⁸ Although the clinical
21 significance of these physiological effects is incompletely understood,
22 accumulating evidence suggests that the supraphysiologic chloride concentration
23 of saline may contribute to kidney injury and impair a patient’s ability to recover
24 from severe illness.⁹⁻¹⁵ The chloride concentration in physiologically balanced
25 crystalloids, such as lactated Ringer’s solution (109 mmol per liter) and Plasma-
26 Lyte A (98 mmol per liter), are more similar to that of human plasma.^{1,2}

27 Previous clinical studies that compared balanced crystalloids and saline have
28 focused on critically ill patients in the ICU and operating room.⁹⁻¹⁸ Although
29 critically ill patients may be the most vulnerable to potential detrimental effects
30 of saline, acutely ill patients without organ failure or other critical illness
31 comprise a large patient population that is routinely treated with intravenous
32 fluids.^{1,19} Owing to the vast number of noncritically ill patients exposed to
33 crystalloids, even small differences in the absolute risk of kidney injury or death
34 between balanced crystalloids and saline may have large public health
35 implications. In the present trial, we investigated the clinical effect of balanced
36 crystalloids versus saline for routine intravenous fluid therapy in the emergency
37 department among noncritically ill adults. We hypothesized that balanced
38 crystalloids would result in earlier hospital discharge and a lower incidence of
39 major adverse kidney events than saline.

1 **Methods**


2 **Trial Design and Oversight**

3 Our trial, the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency
4 Department (SALT-ED) trial, was a single-center, pragmatic, unblinded, multiple-
5 crossover trial that compared balanced crystalloids and saline among
6 consecutive noncritically ill adults treated with intravenous crystalloids in the
7 emergency department before hospitalization outside the ICU. The rationale,
8 design, and statistical analysis plan were prespecified and have been published.²⁰
9 The protocol is also available with the full text of this article at NEJM.org. The
10 institutional review board at Vanderbilt University approved the trial with waiver
11 of informed consent. The trial was monitored by an independent data and safety
12 monitoring board.²⁰ The first and fourth authors vouch for the completeness and
13 accuracy of the data and analyses.

14 **Trial Population**

15 The trial was conducted between January 1, 2016, and April 30, 2017, in the
16 Vanderbilt University Medical Center Adult Emergency Department, a tertiary-
17 care, academic, hospital-based emergency department in the United States with
18 approximately 75,000 visits per year. The trial population consisted of adults
19 (≥ 18 years old) who received at least 500 ml of intravenous isotonic crystalloids
20 in the emergency department and were subsequently hospitalized outside an
21 ICU. Patients who were admitted to an ICU from the emergency department
22 were defined as critically ill and were enrolled in a separate trial that compared
23 balanced crystalloids and saline among critically ill adults, the Isotonic Solutions
24 and Major Adverse Renal Events Trial (SMART), reported in this issue of the
25 *Journal*.¹⁶ Patients who received less than 500 ml of crystalloids in the emergency
26 department were excluded owing to the low dose of exposure to the
27 intervention.¹⁵ The unit of analysis was unique emergency department visit, with
28 individual patients potentially contributing multiple visits. In a sensitivity
29 analysis, we limited the trial population to the first emergency department visit
30 among unique patients.

31 **Treatment Assignments**

32 The trial protocol dictated  the type of isotonic crystalloid that was administered
33 in the emergency department. All other aspects of care were determined by
34 treating clinicians independent of the trial protocol, including whether to treat
35 with crystalloids and the volume of crystalloids administered. Consistent with
36 the concept of a pragmatic clinical trial,²¹ trial procedures were embedded
37 within routine care and executed by clinical personnel.

38 The methods of treatment assignment have been described previously.²⁰ In
39 brief, the type of isotonic crystalloid was assigned according to calendar month,
40 with all patients in the trial emergency department during the same month
41 assigned to the same fluid, either balanced crystalloids or saline. During
42 balanced-crystalloids months, clinicians had the option of choosing either
43 lactated Ringer's solution or Plasma-Lyte A. Clinicians and patients were aware

1 of the treatment assignments. The first trial month was assigned by means of
2 computer-generated simple randomization. Treatment assignments then
3 sequentially crossed over between balanced crystalloids and saline each month
4 for a total of 16 months (Fig. S1 in the Supplementary Appendix, available at
5 NEJM.org). Selection of fluids after the patient's transfer from the emergency
6 department to a hospital floor{q2} was not included as part of the trial
7 intervention.

8 Electronic advisors within the electronic order-entry system informed
9 providers about the trial, asked about relative contraindications to the assigned
10 crystalloid, and guided them through crystalloid orders.²⁰ Relative
11 contraindications to the use of balanced crystalloids included hyperkalemia and
12 brain injury; the severity of hyperkalemia and brain injury at which saline was
13 used instead of balanced crystalloids was determined by the treating provider.
14 There were no relative contraindications listed for saline in the electronic
15 advisor. Providers had the option of ordering off-protocol crystalloids if they
16 believed an alternative was specifically indicated. Patients who received off-
17 protocol fluids were included in the primary analysis according to intention-to-
18 treat principles. In a secondary per-protocol analysis, the population was limited
19 to patients who received all fluids in accordance with the protocol.

20 Data Collection

21 Data were extracted from the electronic medical record. We have previously
22 validated these data-collection techniques for relevant data points.^{15,22,23}
23 Coexisting conditions at baseline were summarized with the Elixhauser
24 Comorbidity Index score.²⁴

25 Outcomes

26 The primary outcome was hospital-free days to day 28, a composite of in-
27 hospital death and hospital length of stay defined as the number of days alive
28 and out of the hospital between the index emergency department visit and 28
29 days later.^{20,25} Patients who died during the index hospitalization and those
30 hospitalized for more than 28 days were classified as having zero hospital-free
31 days. For patients discharged alive before day 28, hospital-free days were
32 calculated as 28 minus length of stay.


33 The trial included three key secondary outcomes: major adverse kidney events
34 within 30 days, acute kidney injury of stage 2 or higher, and in-hospital death.
35 Major adverse kidney events within 30 days was a composite of death, new renal-
36 replacement therapy, or persistent renal dysfunction (final serum creatinine
37 concentration, $\geq 200\%$ of the baseline value) at the earliest of hospital discharge
38 or 30 days after the index emergency department visit (Table S1 in the
39 Supplementary Appendix).²⁶ Stage 2 or higher acute kidney injury was defined
40 according to Kidney Disease: Improving Global Outcomes (KDIGO) creatinine
41 criteria as a maximum serum creatinine concentration at least 200% of the
42 baseline value, an increase in the serum creatinine concentration to at least 4
43 mg per deciliter (354 μmol per liter) with an absolute increase of at least 0.5 mg

1 per deciliter ($44 \mu\text{mol}$ per liter), or initiation of new renal-replacement therapy
2 before the earliest of hospital discharge or 30 days after the index emergency
3 department visit.²⁷ In-hospital death was defined as death before hospital
4 discharge, regardless of hospital length of stay.

5 Patients with end-stage renal disease who were receiving long-term renal-
6 replacement therapy at presentation were not eligible to meet renal outcomes,
7 including new renal-replacement therapy, persistent renal dysfunction, and acute
8 kidney injury. However, patients with end-stage renal disease could meet the
9 outcome of major adverse kidney events within 30 days through death. The
10 baseline creatinine value was defined as the lowest recorded value within the
11 electronic medical record at the trial institution in the year before presentation
12 in the emergency department. Patients with no recorded creatinine values in the
13 previous year had a baseline creatinine value calculated under the assumption of
14 normal baseline renal function with the use of the following equation:
15 $[\text{creatinine (in milligrams per deciliter)} = 0.74 - 0.2 \text{ (if patient is female)} + 0.08 \text{ (if}$
16 $\text{patient is black)} + 0.003 \times \text{age (in years)}]$.²⁸ The serum creatinine concentration in
17 the emergency department was defined as the first recorded value during the
18 index emergency department visit. Creatinine values in the emergency
19 department were considered to be baseline characteristics, whereas creatinine
20 values after hospital admission were considered outcomes. Major adverse kidney
21 events within 30 days and acute kidney injury were calculated on the basis of
22 creatinine values after admission. Patients who presented to the emergency
23 department with a creatinine value that met the criteria for acute kidney injury
24 and who then had a drop in creatinine such that no value after hospital
25 admission met these criteria did not have an outcome of acute kidney injury for
26 the purposes of this trial. Additional, exploratory outcomes are described in
27 Table S2 in the Supplementary Appendix.

28 **Statistical Analysis**

29 A trial duration of 16 months was selected to ensure numerous alternating
30 periods of balanced crystalloids and saline, enrollment throughout the academic
31 and calendar year, coordination with the concomitant trial (SMART),¹⁶ and
32 adequate sample size (power) to balance baseline characteristics and detect at
33 least a 0.5-day difference in hospital-free days between groups. Sample size was
34 dependent on the number of patients treated with isotonic crystalloids in the
35 trial emergency department and hospitalized outside an ICU during the
36 16-month trial period. All the patients who met these criteria were enrolled. On
37 the basis of historical data from the trial emergency department, we estimated
38 that approximately 14,000 patients would be enrolled in 16 months, with the
39 saline group having a mean (\pm SD) of 24 ± 4 hospital-free days. Under these
40 assumptions, 14,000 patients would provide more than 90% power to detect a
41 difference of 0.5 hospital-free days between groups with a type I error rate of
42 0.05. One interim analysis was completed by the data and safety monitoring
43 board at the midpoint of enrollment, which resulted in a recommendation to
44 continue enrollment for the planned 16 months.²⁰

1  Intention-to-treat analysis of eligible patients who were assigned to
2 balanced crystalloids or saline was completed for the primary and secondary
3 outcomes. Hospital-free days were analyzed with a multivariable proportional-
4 odds model. Major adverse kidney events within 30 days, acute kidney injury,
5 and in-hospital death were analyzed with multivariable logistic-regression
6 models. Each model was adjusted for the following baseline characteristics: age,
7 sex, race, admitting inpatient service, and days elapsed since the initiation of the
8 trial.²⁰

9 Heterogeneity of treatment effect was evaluated by adding an interaction
10 term²⁹ to the models between trial-group assignment and each of the following
11 prespecified baseline characteristics: serum creatinine, chloride, and bicarbonate
12 concentrations in the emergency department; age; hospital admission service;
13 and volume of crystalloid administered in the emergency department. A per-
14 protocol secondary analysis was performed that included patients treated
15 exclusively with the assigned crystalloid in the emergency department (100%
16 adherence to trial treatment assignments).

17 A two-sided P value of less than 0.049 was considered to indicate statistical
18 significance for the primary outcome after we accounted for one interim analysis
19 with a Haybittle–Peto boundary of less than 0.001. With the use of the
20 Bonferroni approach, a two-sided P value of less than 0.017 was considered to
21 indicate statistical significance for the three key secondary outcomes: major
22 adverse kidney events within 30 days, acute kidney injury, and in-hospital death.
23 Analyses were conducted with R software, version 3.2.0 (R Foundation for
24 Statistical Computing), and STATA software, version 14 (StataCorp).

25 Results

26 Patients


27 During the 16-month trial, 19,949 patients were treated with isotonic crystalloids
28 in the emergency department and hospitalized; 3689 patients received less than
29 500 ml of crystalloids and were excluded, whereas 2913 patients were admitted
30 from the emergency department to an ICU and enrolled in SMART¹⁶ (Fig. S2 in
31 the Supplementary Appendix). The final sample size was 13,347 patients,
32 including 6708 (50.3%) assigned to balanced crystalloids and 6639 (49.7%)
33 assigned to saline. Baseline creatinine values were calculated for 4666 patients
34 (35.0%) who did not have an available measured value. Baseline characteristics
35 were similar between the two groups, including demographic characteristics,
36 burden of coexisting conditions, admitting service, and renal function (Table 1).

37 Crystalloid Treatment

38 Patients received a median crystalloid volume of 1079 ml (interquartile range,
39 1000 to 2000). Most balanced crystalloids were administered as lactated Ringer's
40 solution (95.3%), with a small percentage administered as Plasma-Lyte A (4.7%).
41 Overall, 88.3% of patients received only the assigned crystalloid in the
42 emergency department with no use of off-protocol crystalloids. The volume of

1 crystalloid that was administered and the adherence to crystalloid assignment
2 were similar in the balanced-crystalloids and saline groups (Table 2, and Fig. S3
3 in the Supplementary Appendix).

4 **Serum Electrolyte Concentrations**

5 At val in the emergency department, serum chloride and bicarbonate
6 concentrations did not differ significantly between patients in the balanced-
7 crystalloids and saline groups. After treatment in the emergency department,
8 patients in the balanced-crystalloids group had lower chloride and higher
9 bicarbonate concentrations than those in the saline group; these differences
10 persisted for several days into the hospitalization (Fig. 1). Hyperchloremia
11 (serum chloride concentration, >110 mmol per liter) and acidemia (serum
12 bicarbonate concentration, <20 mmol per liter) were less common after
13 treatment with balanced crystalloids than with saline (Table S3 in the
14 Supplementary Appendix).

15 **Intention-to-Treat Analysis**

16 There was no difference in the number of hospital-free days between patients in
17 the balanced-crystalloids and saline groups (median, 25 days in each group;
18 adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval
19 [CI], 0.92 to 1.04; P=0.41) (Table 3, and Fig. S4 in the Supplementary Appendix).
20 Patients in the balanced-crystalloids group had a lower incidence of major
21 adverse kidney events within 30 days than those in the saline group (4.7% vs.
22 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01). A lower count for
23 each component of major adverse kidney events — death, renal-replacement
24 therapy, and persistent renal dysfunction — in the balanced-crystalloids group
25 contributed to the lower incidence of the composite outcome (Table 3, and Fig.
26 S5 in the Supplementary Appendix). Stage 2 or higher acute kidney injury
27 occurred in 8.0% of patients in the balanced-crystalloids group and 8.6% of
28 patients in the saline group (adjusted odds ratio, 0.91; 95% CI, 0.80 to 1.03;
29 P=0.14). Other clinical outcomes did not differ significantly between the two
30 groups (Table S3 in the Supplementary Appendix).

31 **Heterogeneity of Treatment Effect**

32 Hospital-free days were similar for patients in the balanced-crystalloids and
33 saline groups across a broad range of baseline characteristics (Fig. 2). Patients
34 who presented to the emergency department with renal dysfunction (serum
35 creatinine concentration, ≥ 1.5 mg per deciliter [$133 \mu\text{mol}$ per liter]) or
36 hyperchloremia (serum chloride concentration, >110 mmol per liter) appeared to
37 have the largest benefit from balanced crystalloids for avoiding major adverse
38 kidney events within 30 days and acute kidney injury. Among patients who
39 presented to the emergency department meeting KDIGO criteria for stage 2 or
40 higher acute kidney injury (1274 patients), resolution of acute kidney injury
41 during hospitalization was more common with balanced crystalloids, as shown
42 by a lower incidence of major adverse kidney events within 30 days in the
balanced-crystalloids group (28.0%) than in the saline group (37.6%) (P<0.001).

1 Sensitivity and Per-Protocol Analyses

2 Sensitivity analyses that were adjusted for period effect and that limited the trial
3 population to patients without end-stage renal disease at presentation in the
4 emergency department (13,112 patients), to patients with a measured baseline
5 serum creatinine value (8681 patients), and to the first emergency department
6 visit among unique patients in the trial (10,573 patients) all produced results
7 similar to those of the primary analysis (Table S4 in the Supplementary
8 Appendix). The per-protocol analysis (11,780 patients) also produced similar
9 results (Tables S5 and S6 in the Supplementary Appendix).

10 Discussion

11 In this pragmatic trial of noncritically ill adults treated with intravenous fluid in
12 the emergency department, treatment with balanced crystalloids did not result in
13 a shorter time to hospital discharge (hospital-free days) than treatment with
14 saline but did result in a lower incidence of the composite of death, new renal-
15 replacement therapy, and persistent renal dysfunction (major adverse kidney
16 events within 30 days), which was a secondary outcome. The lower incidence of
17 major adverse kidney events within 30 days in the balanced-crystalloids group is
18 consistent with the results of SMART, which was conducted concurrently in
19 critically ill adults.¹⁶

20 Patients in the present trial had lower risks of renal outcomes and death
21 overall than critically ill adults requiring ICU admission.^{10,15,16,30} Despite these
22 lower risks, there was an absolute difference of 0.9 percentage points in the risk
23 of major adverse kidney events within 30 days in favor of the balanced-
24 crystalloids group, corresponding to a number needed to treat of 111. Although
25 this risk difference is modest for each patient, implications on a population level
26 may be substantial owing to the millions of patients who receive isotonic
27 crystalloids annually.^{1,19} Operationally, lactated Ringer's solution and saline are
28 similar in terms of cost, availability, and procedures for administration.^{2,31}

29 A strength of our trial was high adherence to the assigned crystalloid group.
30 Use of an unblinded, pragmatic design in a learning health care system³²
31 facilitated incorporation of the trial into routine practice, allowing the assigned
32 crystalloid to be systematically used for early fluid resuscitation immediately
33 after arrival in the emergency department.

34 Limitations of the trial include its single-center setting, unblinded design,
35 and outcome ascertainment that was limited to the index hospitalization. Owing
36 to the pragmatic design that used data collection from the electronic medical
37 record, more detailed information about patient characteristics was not available.
38 In addition, crystalloids ~~that were~~ used for intravenous fluid therapy in the
39 emergency department were included in the trial intervention, but fluids ~~that~~
40 ~~were~~ administered after hospital admission and those used as medication
41 carriers were not controlled. Lactated Ringer's solution represented more than
42 95% of the balanced crystalloids used in the trial; additional study is required to
43 compare Plasma-Lyte A with both saline and lactated Ringer's solution. Last,

1 this trial evaluated balanced crystalloids versus saline as the routine, first-line
 2 isotonic fluid in a broad patient population; fluid selection that is tailored to
 3 specific patient characteristics is an alternative approach that was not evaluated
 4 in this trial.

5 In conclusion, in this pragmatic clinical trial involving noncritically ill adults
 6 treated with intravenous fluids in the emergency department, the number of
 7 hospital-free days, the primary outcome of the trial, did not differ between
 8 patients assigned to balanced crystalloids and those assigned to saline.

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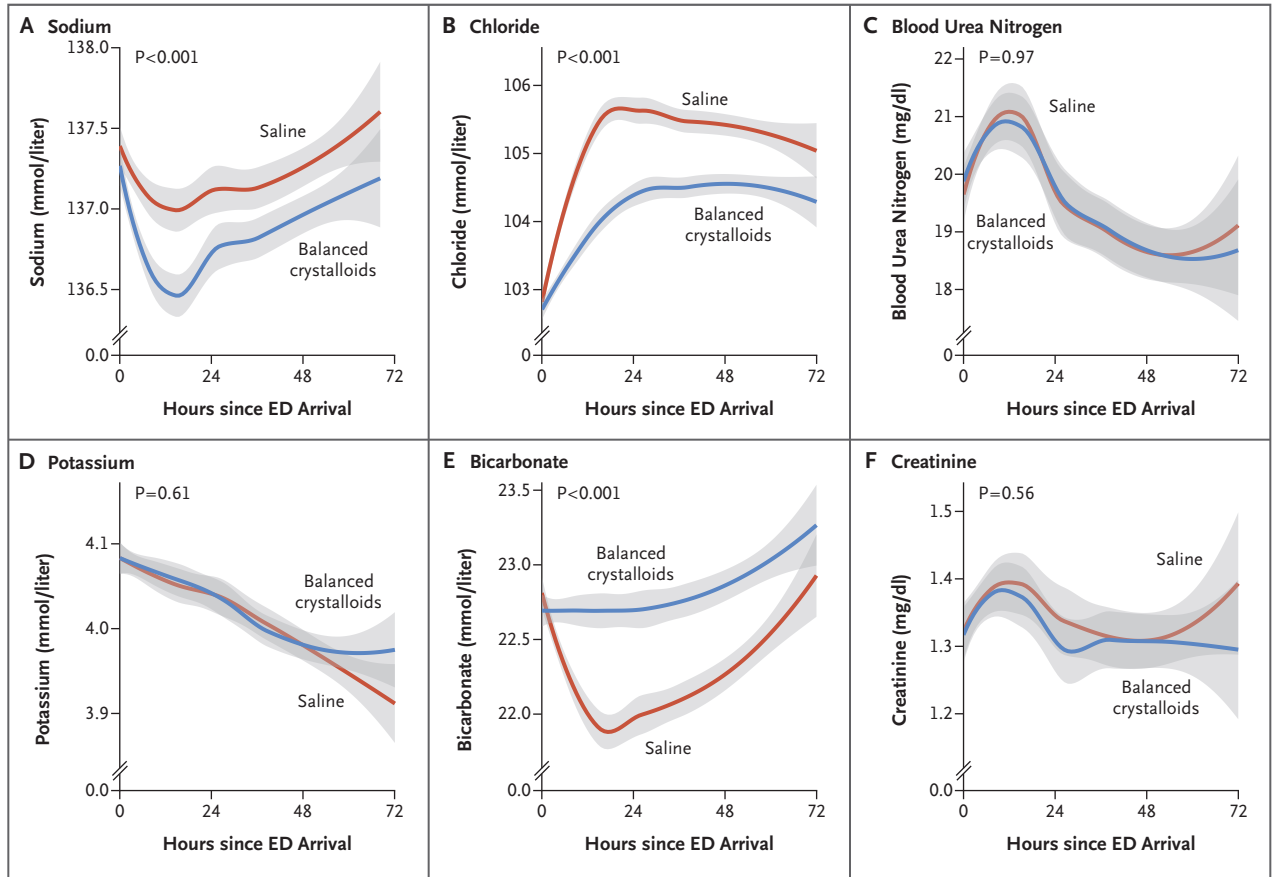


Figure 1. Serum Electrolyte Concentrations at Arrival in the Emergency Department (ED) and in the Subsequent 72 Hours.

Lines and bands represent means and 95% confidence intervals, respectively. Plots were generated with the use of locally weighted scatterplot smoothing. The P values in the figure represent the overall difference between groups, calculated with the use of proportional-odds models. Over time, the separation between groups increased for chloride ($P < 0.001$ for interaction) and bicarbonate ($P < 0.001$ for interaction); interaction terms for the other variables were not significant. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

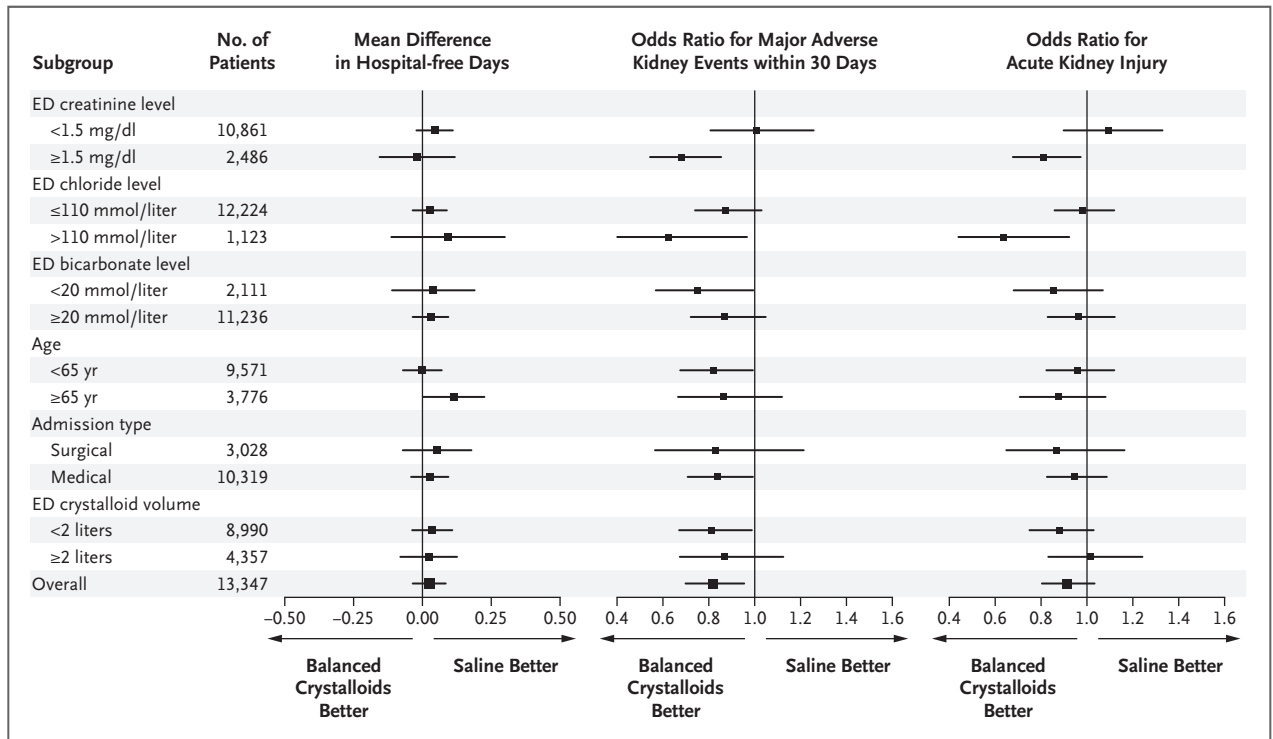


Figure 2. Heterogeneity of Treatment Effect.

Shown are forest plots for hospital-free days to day 28, major adverse kidney events within 30 days, and acute kidney injury of stage 2 or higher according to Kidney Disease: Improving Global Outcomes creatinine criteria. The outcome of major adverse kidney events within 30 days was a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as elevation of creatinine level ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of arrival in the emergency department (235 patients) were not eligible for the outcome of acute kidney injury; hence, the total sample size for the analysis of acute kidney injury was 13,112.

Table 1. Baseline Characteristics.*

Characteristic	Balanced Crystalloids (N = 6708)	Saline (N = 6639)
Median age (IQR) — yr	54 (37–67)	53 (37–67)
Female sex — no. (%)	3507 (52.3)	3379 (50.9)
Race — no. (%)†		
White	5159 (76.9)	5189 (78.2)
Black	1335 (19.9)	1251 (18.8)
Other	214 (3.2)	199 (3.0)
Median Elixhauser Comorbidity Index score (IQR)‡	7 (3–14)	7 (3–14)
Admission service — no. (%)		
Medicine services		
General medicine	4747 (70.8)	4687 (70.6)
Cardiology	303 (4.5)	321 (4.8)
Neurology	117 (1.7)	144 (2.2)
Surgery services		
General surgery	1278 (19.1)	1211 (18.2)
Trauma	263 (3.9)	276 (4.2)
Median baseline serum creatinine (IQR) — mg/dl	0.84 (0.71–0.95)	0.85 (0.71–0.94)
Source of baseline creatinine — no. (%)		
Measured value in medical record	4405 (65.7)	4276 (64.4)
Calculated value by equation	2303 (34.3)	2363 (35.6)
Initial kidney function in ED		
Serum creatinine		
Mean — mg/dl	1.32±1.11	1.31±1.36
Median (IQR) — mg/dl	0.93 (0.77–1.33)	0.93 (0.77–1.32)
≥1.5 mg/dl — no. (%)	1246 (18.6)	1240 (18.7)
End-stage renal disease with long-term renal-replacement therapy — no. (%)	126 (1.9)	109 (1.6)
Stage 2 or higher acute kidney injury — no./total no. (%)§	643/6582 (9.8)	631/6530 (9.7)
Initial serum electrolytes in ED		
Sodium — mmol/liter	137.4±4.3	137.2±4.2
Chloride — mmol/liter	103.1±5.6	102.8±5.4
Potassium — mmol/liter	4.1±0.7	4.1±0.7
Bicarbonate — mmol/liter	22.8±3.7	22.7±3.8
Blood urea nitrogen — mg/dl	20±16	20±16

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two groups, except for first measured sodium ($P=0.006$) and chloride ($P=0.003$). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. ED denotes emergency department, and IQR interquartile range.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ The Elixhauser Comorbidity Index score summarizes the burden of a patient's coexisting conditions. Scores range from –19 to 89, with higher scores indicating a profile of coexisting conditions that is more strongly associated with in-hospital death.²⁴

§ Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of ED arrival were not eligible for the outcome of acute kidney injury.

Table 2. Crystalloids Received in the Emergency Department According to Assigned Treatment Group.*

Variable	Balanced Crystalloids (N = 6708)	Saline (N = 6639)
Total crystalloid volume		
Mean — ml	1608±1095	1597±1105
Median (IQR) — ml	1089 (1000–2000)	1071 (1000–2000)
≥2000 ml — no. (%)	2207 (32.9)	2150 (32.4)
Median volume of balanced crystalloids (IQR) — ml	1000 (1000–2000)	0
Median volume of saline (IQR) — ml	0	1000 (1000–2000)
Percentage of crystalloid volume consistent with assigned group — no. (%)		
100%: Per-protocol population	5620 (83.8)	6160 (92.8)
51–99%	514 (7.7)	270 (4.1)
1–50%	254 (3.8)	131 (2.0)
0%	320 (4.8)	78 (1.2)

* Plus-values are means ±SD. Percentages may not sum to 100 because of rounding.


Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

Outcome	Balanced Crystalloids (N = 6708)	Saline (N = 6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

* Multivariable models were adjusted for age, sex, race, admitting service, and time (days since trial initiation).

† Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of emergency department arrival (126 in the balanced-crystalloids group and 109 in the saline group) were not eligible for the following outcomes: new renal-replacement therapy within 30 days, final serum creatinine concentration within 30 days at least 200% of the baseline value, and stage 2 or higher acute kidney injury.

Queries

q1. AU: Affiliations have been reordered; please check carefully. 

q2. AU: OK as edited. 