Supplemental Online Content

Zampieri FG, Machado FR, Biondi RS, et al; for the BaSICS investigators and the BRICNet members. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: the BaSICS randomized clinical trial. *JAMA*. Published online August 10, 2021. doi:10.1001/jama.2021.11684

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

eMethods

Additional Trials Procedures Information

Overview of BaSICS trial: BaSICS was a large factorial pragmatic trial. Patients were randomized to two different intervention arms. The first was the comparison between balanced solution versus 0.9% saline as preferred fluid for resuscitation, maintenance and dilutions in critically ill patients. The second arm compared two different infusion speeds (333 mL/h – "slow" versus "control" 999 mL/h). The randomization scheme is shown in eFigure 1.

Fluids were labeled A, B, C… F. Therefore, a given patient could be randomized to B-slow, meaning we should receive "B" labeled fluids as discussed below and, in case of need for fluid challenge, a speed of 333 mL/h should be used. All fluid challenges, maintenance fluids and dilutions (above 100 mL) were requested to be performed using the trial fluids during ICU stay, up to 90 days after enrollment (see eFigure 2).

Sites received a list of all medications that were compatible with both 0.9% saline and the balanced solution. This list included several sedative agents (including midazolam, fentanyl), vasoactive drugs (inotropes and vasopressors, including dobutamine, dopamine, norepinephrine, epinephrine, etc.), and antibiotics. For drugs compatible with both 0.9% saline and the balanced solution, sites were instructed to use the allocated fluid group as diluent. At the end of enrollment, we surveyed the local principal investigators or the researcher that was directly involved in enrolling and following up patients at their sites on whether they could guess which letters were each fluid type. We received 66 answers from the 75 sites; 6 responses fully guessed the association between letters and fluid types, a result that was still compatible with the null hypothesis that the results were random (p=0.214).

Decision to submit two separated manuscripts: As discussed in the protocol, since study inception we planned to publish the two arms in BaSICS as separated manuscript if there was no interaction between both interventions.

Screening log: BaSICS was a large pragmatic trial. We expected that many of the patients admitted to the ICU would fulfill eligibility criteria. Demanding a detailed screening log from all sites would be impractical. Therefore, we only have information available from eligible patients.

Additional definition details

Presence of sepsis at enrollment: We asked sites whether the patient filled sepsis criteria at enrollment, defining sepsis as presence of suspected infection plus organ failure with a SOFA score of at least two, or increase in baseline SOFA, as per Sepsis 3. We did not collect data on infection source.

Reference: Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574.

Traumatic Brain Injury: This was a simple pragmatic question noted on the CRF as whether the patient had TBI at admission or not. No details on mechanisms of trauma, type of brain injury or other information, including intracranial pressure, were collected.

Acute Kidney Injury: We defined acute kidney injury based on a slightly modified Kidney Disease Improving Global Outcomes (KDIGO) definition. We defined AKI (KDIGO equal or above 2) if there was a twofold or higher increase in serum creatinine level from reference level, or urine output level < 0.5 mL/kg/h based on 24h average (which is different from traditional KDIGO assessment; urinary output was collected daily at days 1, 2, 3 and 7). If both urinary output and creatinine were available, the worse was used for defining KDIGO. The reference creatinine level, in order of preference, was a previous creatinine levels (the most recent value available in the previous 6 months and before current admission) followed by an estimated baseline creatinine using the Modification of Diet in Renal Disease equation: Creatinine level = 75 / (186 * [age – 0.203] * F * B) – 0.887, where F = 0.742 (female patients) and B = 1.21 (black patients). KDIGO analyses excluded patients enrolled with KDIGO $\geq$ 2.

Reference: Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013; 17: 204.

Missing values and imputation

The following variables had missing values that were imputed for Table 1:

1. Previous creatinine: 5,440 of 10,520 patients had a previous creatinine measurement; for 5,080 patients' previous creatinine was calculated using Modification of Diet in Renal Disease equation as specified in the protocol. These values were used as reference for KDIGO calculation during ICU stay for Days 3 and 7 endpoints.

2. Randomization (baseline) creatinine: Creatinine at enrollment was missing for 383 patients. For 297 of those patients, creatinine was available at day 1; in this scenario, we defined the randomization creatinine as Day 1 creatinine. For the remaining 86 patients; multiple imputation was performed. These randomization creatinine values were used only for defining subgroups.
3. Baseline SOFA: There were 54 missing baseline SOFA values. These values were imputed.
4. Age: There were no missing values
5. Sex: Missing in 36 patients. These values were imputed.
6. Hypotension at enrollment: This information was missing in 29 patients. These values were imputed.
7. Mechanical Ventilation at enrollment: Missing in 27 patients. These values were imputed. Imputed cases were not used for the secondary endpoint of mechanical ventilation-free days.
8. Traumatic Brain Injury: This information was missing for 27 patients. These values were imputed.
9. Baseline heart failure and cirrhosis: Both missing in 27 patients. These values were imputed.
10. Fluid use in the 24h before enrollment: Missing in 28 patients. These values were imputed.
11. Time between ICU admission and enrollment: Missing for 26 patients. These values were imputed.
12. Admission type (planned or unplanned): There were 28 missing values. These values were imputed.
13. 90-day mortality: There were 15 missing values that were imputed.

Imputation procedures: Imputation was made in a single model in {mice} using age, sex, enrolling site, randomization creatinine, SOFA, admission type, use of fluid in the 24 hours before enrollment, presence of heart failure or cirrhosis, traumatic brain injury at enrollment, hypotension at enrollment, mechanical ventilation at enrollment, and outcome. Five imputations sets were obtained, and the median of the imputed results (or the most frequent category) were used for analysis. Time from ICU admission and randomization was imputed using median value (which was zero). Reference: Stef van Buuren, Karin Groothuis-Oudshoorn (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1-67. URL https://www.jstatsoft.org/v45/i03/.

Sensitivity and Exploratory Analysis

Several exploratory analyses were performed and are discussed below

A. Only patients with known outcome (complete case analysis): There were no significant differences in the primary endpoint when we excluded patients with missing primary endpoint information. Hazard Ratio 0.97 (95% CI 0.9 to 1.05; p value 0.49).

B. Only patients that did not receive fluids before enrollment: There was no significant differences in the primary endpoint when we considered only patients that did not receive fluid prior to ICU admission (611/1661 - 36.8% - versus 636/1671 - 38.1% - for Balanced Solution versus 0.9% saline; HR 0.98 [0.88 to 1.1], p = 0.74).

C. Composite mortality and renal replacement therapy in the hospital (eTable 6)

D. Composite mortality or death in the hospital or doubling creatinine at days 1, 2, 3 or 7: This analysis was made to mimic MAKE30 endpoint in SMART trial. We, however, only had creatinine values collected on specific days. In this analysis, no difference could be found between both groups: 1,452/5,218 (27.8%) in Balanced solution group and 1,527/5,287 (28.9%) in 0.9% saline group. Odds ratio: 0.95 [0.86 - 1.04], p=0.277

E. 90-day survival according to baseline KDIGO using a different stratification (0, 1 and 2-3) (eTable 7)

F. Acute kidney injury: We performed several sensitivity analysis for acute kidney injury considering: (1) Only creatinine for diagnosis of acute kidney injury (which also considered only patients with enrollment KDIGO < 2; (2) A complete case analysis with only patients with known previous creatinine before hospital admission; (3) Using randomization creatinine as baseline for KDIGO calculation; (4) including all patients regardless of baseline KDIGO, and (4) A continuous creatinine level assessment from days 1, 2, 3 and 7. One of the pre-planned subgroups included patients with KDIGO 1 and > 2 at enrollment, which was defined exclusively based on creatinine criteria at enrollment (1.5-1.9 times increase or an absolute increase greater than 0.3 mg/mL for KDIGO 1 and at least 2 times increase for KDIGO 2). Results for analysis (1), (2) and (3) are shown in eTable 8 and results for analysis (5) are shown in eFigures 5 and 7. Results for creatinine and diuresis over time (5).

C. Excluding patients with traumatic brain injury (eTable 9).

D. Primary endpoint according to baseline chloride values (eTable 4).

E. Bayesian Network for Analysis of important competing events

As a sensitivity analysis, we planned to use a Bayesian network to address conditional probabilities of relevant outcomes regarding organ dysfunction while accounting for competing risks and conditional probabilities. We defined the following network for this sensitivity analysis (eFigure 4).

That is, baseline use of vasopressors (yes/no) and mechanical ventilation (yes/no), as well as baseline Glasgow coma scale (stratified in 15, 14-13, ≤12) were related to the patient being discharged up to day 3 (green spot, top left), dying (red spot, bottom left) or moving to a day 3 status. Thereafter, the same considerations are considered for defining the status on day 7. This Bayesian Network, built with R {bnlearn} package allowed us to explore some additional scenarios, especially those that had borderline significant results (secondary endpoints for neurological and hemodynamic SOFA, reported on Table 2) while accounting for competing risks (patient must be alive and in the ICU at day 7 to have a measured SOFA at day 7). We queried the Bayesian network and obtained 95% credible intervals for conditional probabilities in some scenarios for each fluid type. Odds ratio were calculated from the ratio of each query odds (defined as probability/[1-probability]) and summarized as median and 95% credible intervals. Credible intervals were obtained through 1,000 bootstraps. Some results are shown in eTable 5.

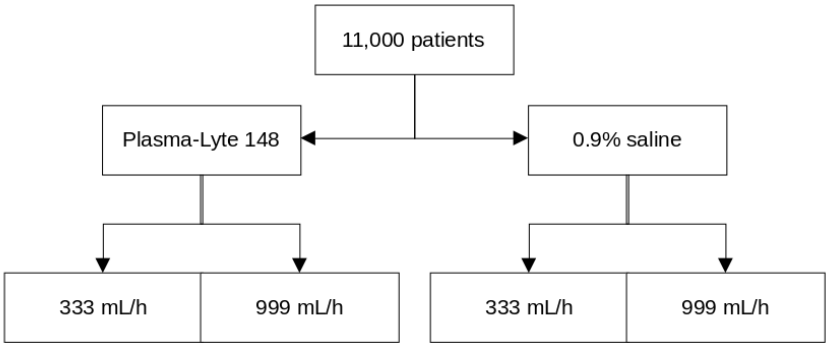
This alternative analysis does not support harms for Balanced solution in terms of hemodynamic effect. Regarding neurological outcomes, we still found a high probability that Balanced solution was associated with a higher probability of lower Glasgow Coma Scale (below or equal to 12) for patients that were mechanically ventilated at day 7 given that patient was admitted on mechanical ventilation and remained on mechanical ventilation until day 7. The use of Glasgow Coma Scale is one of the limitations of this analysis, since it can be confounded by sedation, among other factors. We instructed sites to note in the CRF the GCS before intubation and to report the same GCS until they felt assessing GCS was possible due to sedation weaning. However, we advise caution when interpreting these results.

A similar statistical analysis has been previously published:

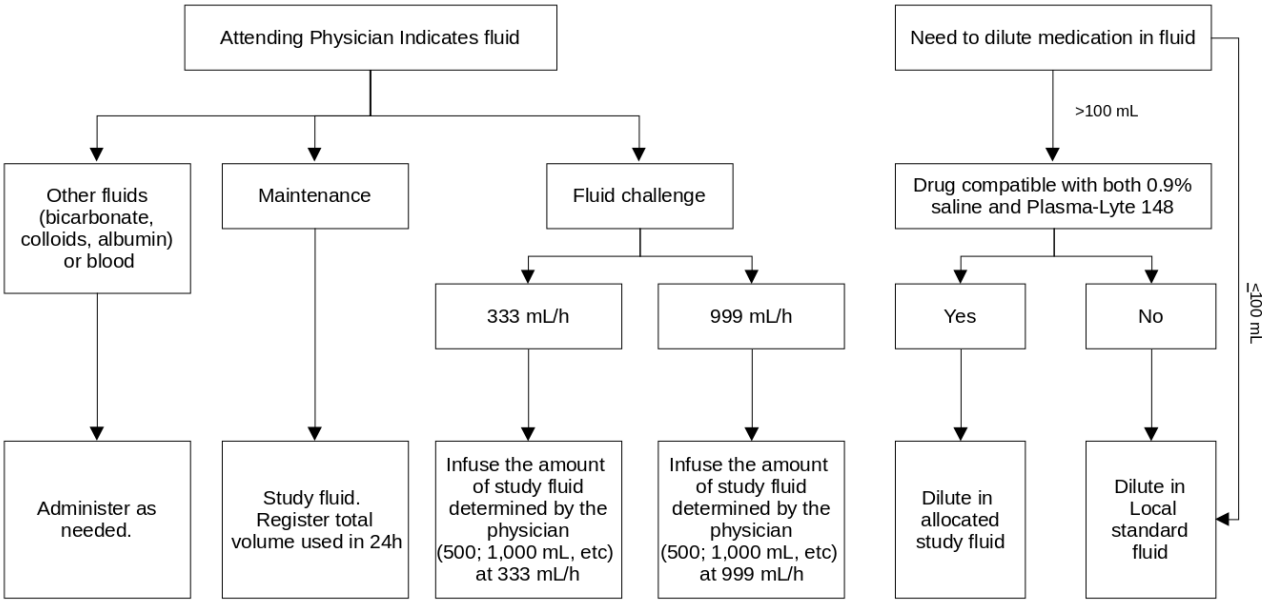
- Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, Hernandez G. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status versus Serum Lactate Levels among Patients with Septic Shock. A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med. 2020 Feb 15;201(4):423-429. doi: 10.1164/rccm.201905-0968OC. PMID: 31574228. and

- Zampieri FG, Aguiar FJ, Bozza FA, Salluh JIF, Soares M; ORCHESTRA Study Investigators. Modulators of systemic inflammatory response syndrome presence in patients admitted to intensive care units with acute infection: a Bayesian network approach. Intensive Care Med. 2019 Aug;45(8):1156-1158. doi: 10.1007/s00134-019-05595-0. Epub 2019 Mar 13. PMID: 30868180.

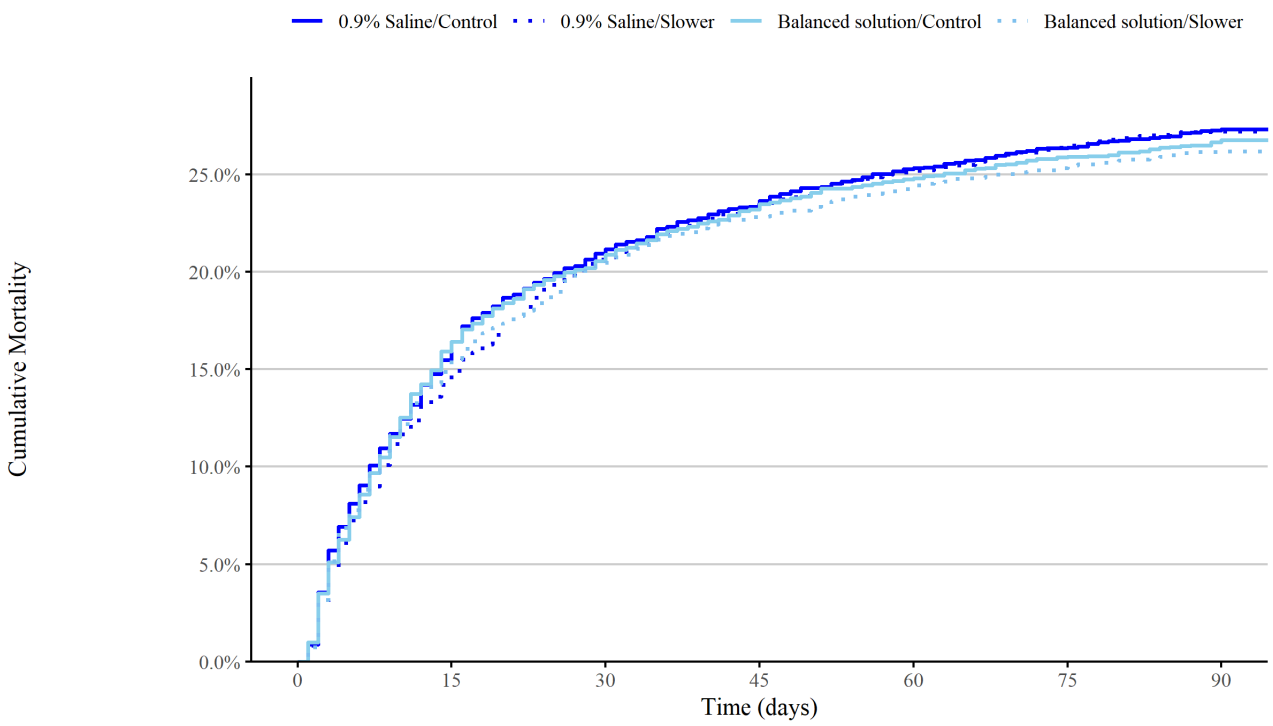
eFigure 1. Study scheme



eFigure 2. Fluid management in BaSICS



eFigure 3. Primary outcome results according to both interventions in BaSICS (infusion speed and fluid type)

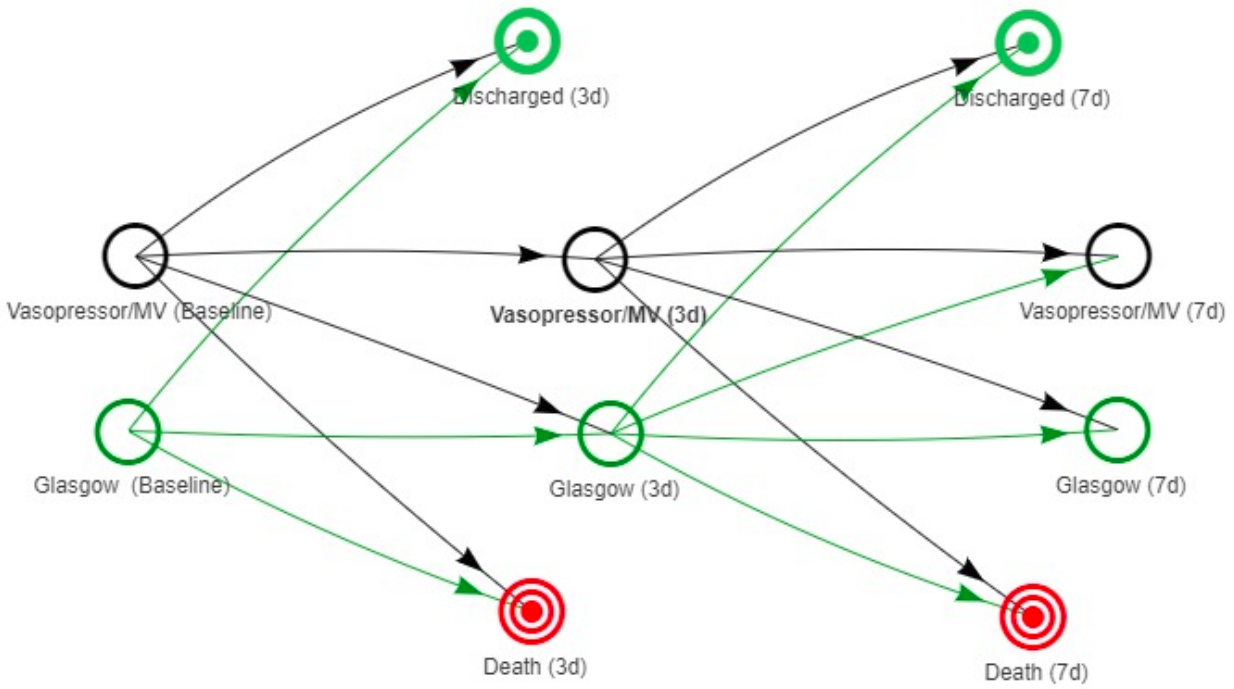


Patients at risk

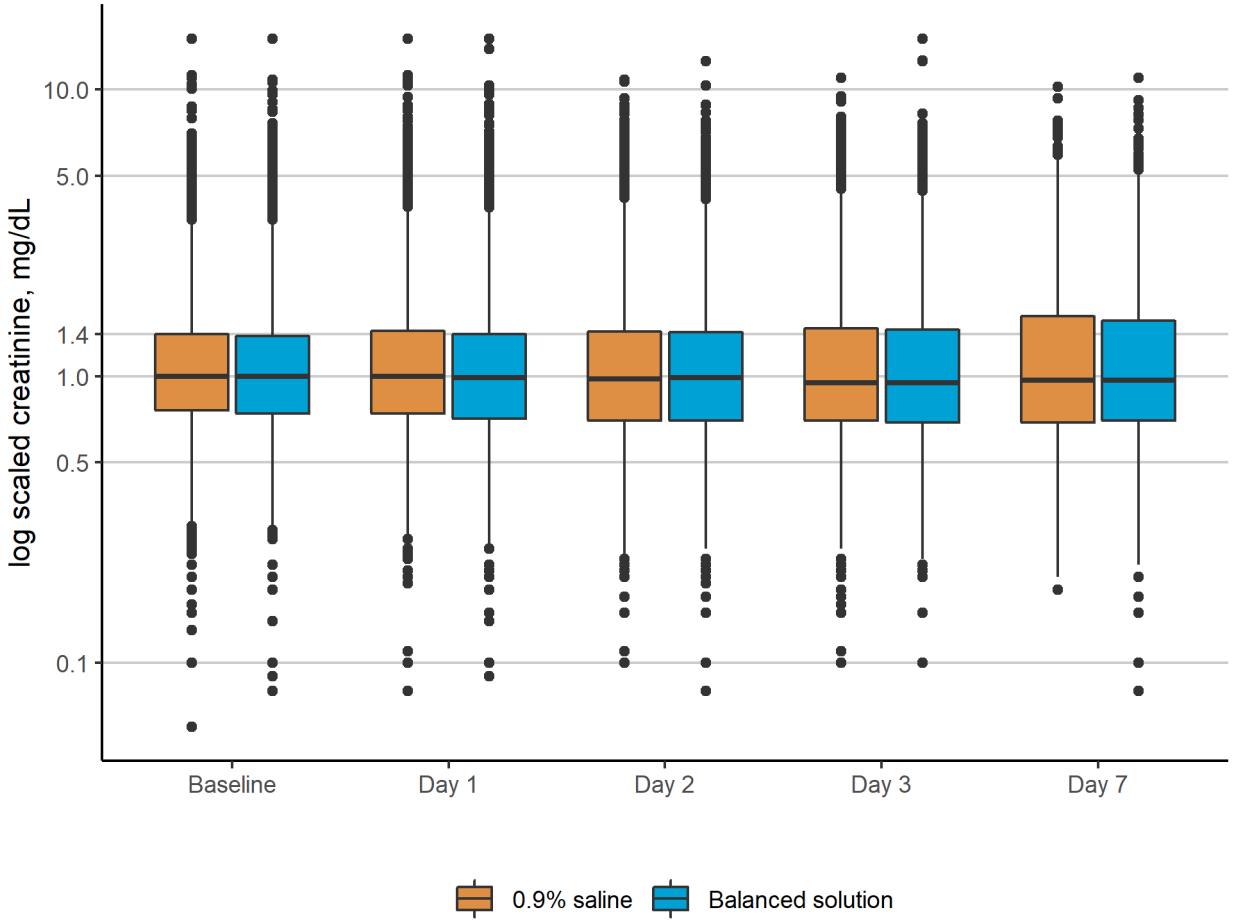
0.9% Saline/Control	2641	2224	2078	2013	1962	1934	1910
0.9% Saline/Slower	2649	2268	2094	2021	1975	1941	1919
Balanced solution/Control	2603	2182	2060	1991	1951	1920	1899
Balanced solution/Slower	2627	2225	2079	2013	1971	1943	1922

P value for interaction 0.98

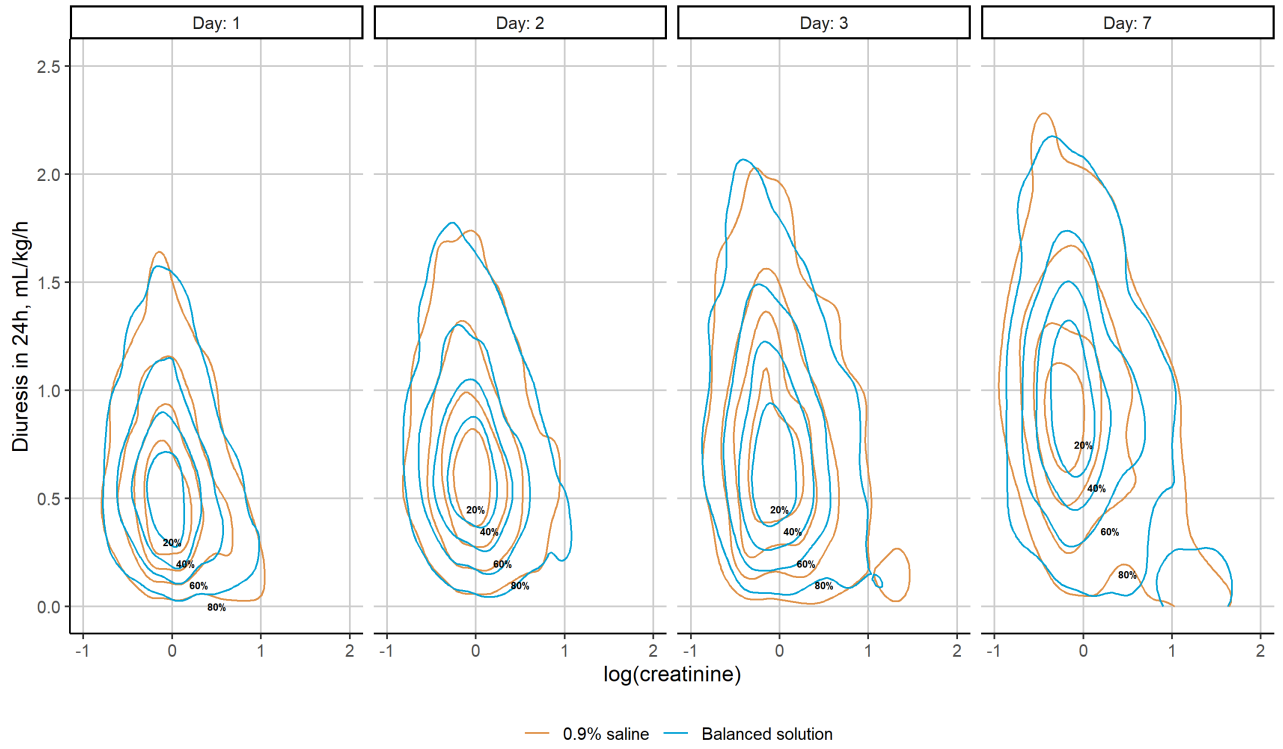
eFigure 4. Bayesian Network



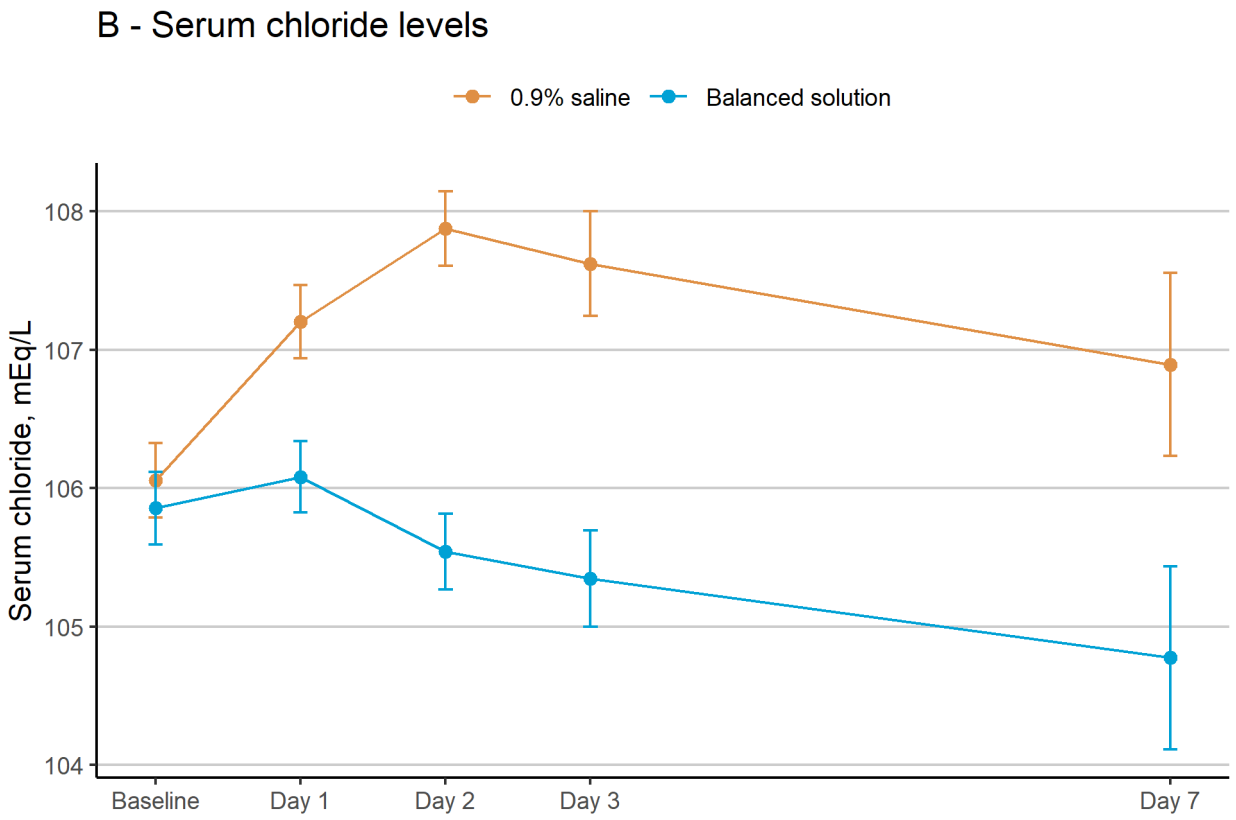
eFigure 5. Creatinine values at the measured days according to group



eFigure 6. Density plot of creatinine (in log values, x-axis) and diuresis (y-axis) values at the measured days (panels) according to group



eFigure 7. Chloride levels over time displayed at mean and standard deviation



P<.001 for the difference.

eTable 1. Baseline characteristics of the included patients on the four groups of the trial

Characteristics	Balanced solution / Slow infusion rate	Balanced solution / Control infusion rate	0.9% sodium chloride/ Slow infusion rate	0.9% sodium chloride / Control infusion rate
	n = 2627	n = 2603	n = 2649	n = 2641
Age - mean (SD)	60.5 (17.1), n=2627	61.4 (17.0), n=2603	61 (17.0), n=2649	61.5 (16.8), n=2641
Female sex - no./total no. (%)	1200/2627 (45.7%)	1121/2603 (43.1%)	1160/2649 (43.8%)	1174/2641 (44.5%)
Source of admission to ICU - no./total no. (%)				
Elective surgery	1256/2616 (48%)	1235/2596 (47.6%)	1313/2644 (49.7%)	1275/2637 (48.4%)
Unplanned admissions	1360/2616 (52%)	1361/2596 (52.4%)	1331/2644 (50.3%)	1362/2637 (51.6%)
Non-elective surgery	326/2616 (12.5%)	327/2596 (12.6%)	325/2644 (12.3%)	327/2637 (12.4%)
Emergency Department	574/2616 (21.9%)	620/2596 (23.9%)	577/2644 (21.8%)	611/2637 (23.2%)
Ward	289/2616 (11.0%)	260/2596 (10.0%)	254/2644 (9.6%)	253/2637 (9.6%)
Another hospital	154/2616 (5.9%)	134/2596 (5.2%)	151/2644 (5.7%)	155/2637 (5.9%)
Another ICU	17/2616 (0.6%)	20/2596 (0.8%)	24/2644 (0.9%)	16/2637 (0.6%)
APACHE II - median (IQR)	12 [8 - 16], n=2609	12 [8 - 17], n=2586	12 [8 - 17], n=2639	12 [8 - 17], n=2632
SOFA score - median (IQR)	4 [2 - 6], n=2609	4 [2 - 7], n=2586	4 [2 - 7], n=2639	4 [2 - 7], n=2632
KDIGO criteria for acute kidney injury > = 1	813/2609 (31.2%)	870/2589 (33.6%)	882/2638 (33.4%)	883/2627 (33.6%)
Sepsis	467/2616 (17.9%)	499/2596 (19.2%)	497/2643 (18.8%)	518/2637 (19.6%)
Traumatic brain injury	131/2616 (5%)	116/2596 (4.5%)	120/2644 (4.5%)	116/2637 (4.4%)
Hypotension (MAP < 65 or systolic arterial pressure < 90 or use of vasopressors) - no. (%)	1574/2615 (60.2%)	1587/2596 (61.1%)	1581/2643 (59.8%)	1614/2637 (61.2%)
Mechanical ventilation - no./total no. (%)				
Non-invasive mechanical ventilation >12h	183/2616 (7.0%)	149/2596 (5.7%)	185/2644 (7.0%)	156/2637 (5.9%)
Invasive mechanical ventilation	1149/2616 (43.9%)	1155/2596 (44.5%)	1145/2644 (43.3%)	1195/2637 (45.3%)
Serum creatinine - mg/dL (mean (SD))	1.2 (0.9), n=2600	1.2 (0.9), n=2587	1.2 (0.9), n=2628	1.2 (0.9), n=2619
Creatinine ≤ 1.5 mg/dL	2108/2600 (81.1%)	2031/2587 (78.5%)	2080/2628 (79.1%)	2082/2619 (79.5%)
Creatinine 1.5-2.5	332/2600 (12.8%)	387/2587 (15.0%)	366/2628 (13.9%)	354/2619 (13.5%)
Creatinine > 2.5	160/2600 (6.2%)	169/2587 (6.5%)	182/2628 (6.9%)	183/2619 (7.0%)
Cirrhosis or acute liver failure	55/2616 (2.1%)	77/2596 (3.0%)	61/2644 (2.3%)	73/2637 (2.8%)
Heart failure	281/2616 (10.7%)	312/2596 (12%)	261/2644 (9.9%)	282/2637 (10.7%)
Time from ICU admission to randomization - days, median [percentiles 2.5% - 97.5%]	0 [0 - 1], n=2616	0 [0 - 1], n=2596	0 [0 - 1], n=2645	0 [0 - 1], n=2637

Characteristics	Balanced solution / Slow infusion rate	Balanced solution / Control infusion rate	0.9% sodium chloride/ Slow infusion rate	0.9% sodium chloride / Control infusion rate
	n = 2627	n = 2603	n = 2649	n = 2641
Balanced Crystalloid and Saline Administration in the 24 h Before Enrollment				
Balanced solution				
Proportion of patients who received fluid (balanced solution) - no./total (%)	1231/2616 (47.1%)	1272/2596 (49.0%)	1298/2643 (49.1%)	1263/2637 (47.9%)
Receipt of > 1000ml in the 24h prior to randomization - no./total no. (%)	802/2616 (30.7%)	824/2596 (31.7%)	851/2643 (32.2%)	841/2637 (31.9%)
Fluid volume (balanced solution), median (IQR), mL	0 [0 - 1500], n=2616	0 [0 - 1500], n=2596	0 [0 - 1500], n=2643	0 [0 - 1500], n=2637
Saline				
Proportion of patients who received fluid (Saline) - no./total no. (%)	1025/2616 (39.2%)	962/2596 (37.1%)	1010/2643 (38.2%)	961/2637 (36.4%)
Receipt of > 1000ml in the 24h prior to randomization - no./total no. (%)	471/2616 (18.0%)	464/2596 (17.9%)	507/2643 (19.2%)	487/2637 (18.5%)
Fluid volume (Saline), median (IQR), mL	0 [0 - 1000], n=2616	0 [0 - 1000], n=2596	0 [0 - 1000], n=2643	0 [0 - 1000], n=2637
Total				
Proportion of patients who received fluid (Total) - no./total no. (%)	1785/2616 (68.2%)	1766/2596 (68.0%)	1830/2643 (69.2%)	1779/2637 (67.5%)
Receipt of > 1000ml in the 24h prior to randomization - no./total no. (%)	1158/2616 (44.3%)	1169/2596 (45.0%)	1237/2643 (46.8%)	1190/2637 (45.1%)
Fluid volume (Total), median (IQR), mL	1000 [0 - 2500], n=2616	1000 [0 - 2500], n=2596	1000 [0 - 2500], n=2643	1000 [0 - 2500], n=2637

eTable 2. Adhesion to allocated fluid use

	Balanced solution (n=5230)		0.9% saline (n=5290)	
	Patients (%)	**Amount of infused fluid, ml**	**Patients (%)**	**Amount of infused fluid, ml**
Trial fluid				
Day 1	5,187/5,201 (99.7%)	1,500 [900 – 2,087.5] (n=5,187)	5,256/5,269 (99.8%)	1,500 [919.5 – 2,126] (n=5,256)
Day 2	3,791/4,837 (78.4%)	1,000 [500 – 1,600] (n=3,791)	3,904/4,923 (79.3%)	1,000 [500 – 1,546.5] (n=3,904)
Day 3	2,493/3,829 (65.1%)	633 [365 - 1270] (n=2,493)	2,463/3,879 (63.5%)	625 [357.5 – 1,304] (n=2,463)
Day 7	943/1,557 (60.6%)	550 [280 - 1168.5] (n=943)	939/1,615 (58.1%)	500 [250 – 1,000] (n=939)
Non trial crystalloids				
Day 1	2,730/5,201 (52.5%)	500 [200 - 954] (n=2,730)	2,784/5,269 (52.8%)	500 [200 - 953.2] (n=2,784)
Day 2	2,405/4,837 (49.7%)	500 [220 - 980] (n=2,405)	2,474/4,923 (50.3%)	500 [200 - 990] (n=2,474)
Day 3	1,904/3,829 (49.7%)	400 [186.5 - 750] (n=1,904)	1,936/3,879 (49.9%)	400 [174.8 - 798] (n=1,936)
Day 7	815/1557 (52.3%)	482 [200 - 850] (n=815)	820/1,615 (50.8%)	434 [200 - 802.2] (n=820)
Glucose (5%, 10%)				
Day 1	1,191/5,201 (22.9%)	351 [184 - 677] (n=1,191)	1,174/5,269 (22.3%)	360 [193.8 - 699.5] (n=1,174)
Day 2	1,048/4,837 (21.7%)	420 [200 - 762] (n=1,048)	1,057/4,923 (21.5%)	400 [200 - 750] (n=1,057)
Day 3	824/3,829 (21.5%)	400 [190.5 - 750] (n=824)	808/3,879 (20.8%)	391.5 [200 - 753.2] (n=808)
Day 7	365/1,557 (23.4%)	450 [200 - 819] (n=365)	405/1,615 (25.1%)	434 [200 - 750] (n=405)
Synthetic colloids				
Day 1	46/5,201 (0.9%)	500 [500 - 1000] (n=46)	54/5,269 (1%)	500 [250 - 922.5] (n=54)
Day 2	24/4,837 (0.5%)	261 [250 - 500] (n=24)	32/4,923 (0.7%)	362.5 [250 - 619.5] (n=32)
Day 3	10/3829 (0.3%)	320 [250 - 510] (n=10)	15/3,879 (0.4%)	270 [229.5 - 500] (n=15)
Day 7	6/1557 (0.4%)	362 [267.5 - 851] (n=6)	7/1,615 (0.4%)	351 [143.5 - 936] (n=7)
Albumin				
Day 1	105/5,201 (2%)	100 [100 - 200] (n=105)	121/5,269 (2.3%)	100 [100 - 200] (n=121)
Day 2	91/4,837 (1.9%)	150 [100 - 300] (n=91)	81/4,923 (1.6%)	100 [100 - 200] (n=81)
Day 3	53/3,829 (1.4%)	100 [100 - 350] (n=53)	51/3,879 (1.3%)	150 [100 - 300] (n=51)
Day 7	23/1,557 (1.5%)	150 [100 - 380] (n=23)	19/1,615 (1.2%)	150 [100 - 175] (n=19)
Packed red cells				
Day 1	453/5,198 (8.7%)	2 [1 - 2] (n=453)	420/5,268 (8%)	2 [1 - 2] (n=420)
Day 2	303/4,835 (6.3%)	1 [1 - 2] (n=303)	333/4,922 (6.8%)	1 [1 - 2] (n=333)
Day 3	264/3,825 (6.9%)	1 [1 - 2] (n=262)	279/3,873 (7.2%)	1 [1 - 2] (n=278)
Day 7	62/1,550 (4%)	1 [1 - 2] (n=62)	95/1,613 (5.9%)	1 [1 - 2] (n=95)

eTable 3. Primary outcome model

Coefficient	Estimative	Standard error	HR [95%CI]	p value
Balanced solution group	-0.02	0.05	0.98 [0.88 to 1.08]	0.64
Slow infusion	0.02	0.05	1.02 [0.92 to 1.14]	0.65
Age, per 10 years increment	0.02	0.01	1.22 [1.20 to 1.25]	<0.01
Baseline SOFA, per point	0.15	0.01	1.16 [1.15 to 1.17]	<0.01
Unplanned admission without sepsis	1.03	0.05	2.80 [2.53 to 3.10]	<0.01
Unplanned admission with sepsis	1.22	0.06	3.40 [3.04 to 3.80]	<0.01
Interaction (Balanced solution: Slow infusion)	~0.00	0.08	1.00 [0.86 to 1.16]	0.98

eTable 4. Results for primary endpoint stratified by baseline chloride values (complete case analysis)

Baseline serum chloride	Balanced solution	0.9% saline	Hazard Ratio 95% CI
< 110 mEq/L	360/1616 (22.3%)	364/1597 (22.8%)	0.99 [0.85 to 1.14]
≥ 110 mEq/L	157/451 (34.8%)	172/457 (37.6%)	0.87 [0.7 to 1.08]

P value for interaction 0.37

eTable 5. Results for queries in the Bayesian Network

Query	Probability in Balanced solution [95%CrI]	Probability in 0.9% Saline [95% CrI]	Odds Ratio (PL / Saline) [95% CrI]
Neurological Queries			
Probability that patient has Glasgow ≤ 14 at day 7, given they are still alive in the ICU and that they were not using vasopressors or mechanical ventilation neither at admission nor day 3	0.1 [0.08 - 0.12]	0.11 [0.09 - 0.13]	0.91 [0.71 - 1.12]
Probability that patient has Glasgow ≤ 14 at day 3, given they are alive in the ICU and that they were not using vasopressors or mechanical ventilation at admission	0.19 [0.17 - 0.21]	0.17 [0.15 - 0.19]	1.14 [0.97 - 1.35]
Probability that patient has Glasgow ≤ 12 and is mechanically ventilated at day 7, given they are alive and in the ICU and that they were using mechanical ventilation at admission and at day 3	0.21 [0.19 - 0.23]	0.17 [0.15 - 0.19]	**1.34 [1.08 - 1.6]**
Probability that patient has Glasgow ≤ 12 and is mechanically ventilated at day 3, given they are alive in the ICU and that they were using mechanical ventilation at admission	0.12 [0.11 - 0.13]	0.11 [0.1 - 0.12]	1.11 [0.96 - 1.3]
Hemodynamic Queries			
Probability that patient is using vasopressors at day 3, given they are alive in the ICU and that there were not using vasopressors at admission	0.1 [0.09 - 0.11]	0.09 [0.08 - 0.1]	1.13 [0.96 - 1.34]
Probability that patient is using vasopressors at day 7, given they are alive in the ICU and that there were not using vasopressors at admission and at day 3	0.03 [0.02 - 0.04]	0.03 [0.02 - 0.04]	1.06 [0.76 - 1.43]
Probability that patient is using vasopressors at day 3, given they are alive in the ICU and that there were using vasopressors at admission	0.31 [0.29 - 0.33]	0.3 [0.28 - 0.32]	1.04 [0.92 - 1.19]
Probability that patient is using vasopressors at day 7, given they are alive in the ICU and that there were using vasopressors at admission and at day 3	0.22 [0.19 - 0.24]	0.22 [0.19 - 0.24]	1.02 [0.83 - 1.27]
Probability that patient is using vasopressors at day 7, given they are alive in the ICU and that there were not using vasopressors at admission but were using vasopressor at day 3	0.21 [0.19 - 0.24]	0.19 [0.17 - 0.22]	1.13 [0.89 - 1.39]

eTable 6. Composite endpoint of mortality and use of renal replacement therapy during hospital stay

Use of fluid 24h before enrollment	Balanced Solution	0.9% Saline	Odds Ratio [95% CI]	P value
None	575/1661 (34.6%)	601/1671 (36%)	0.96 [0.82 - 1.12]	0.583
Any	727/3549 (20.5%)	749/3609 (20.8%)	0.98 [0.86 - 1.12]	0.779

p for interaction = 0.82

eTable 7. Primary endpoint analysis according to KDIGO at enrollment

Subgroup	Balanced Solution	0.9% saline	HR [IC95%]
	n= 5230	n= 5290	
KDIGO criteria for acute kidney injury			
0	703/3531 (19.9%)	732/3515 (20.8%)	0.95 [0.86 to 1.06]
1	286/829 (34.5%)	263/835 (31.5%)	1.08 [0.91 to 1.28]
2-3	392/870 (45.1%)	444/940 (47.2%)	0.97 [0.85 to 1.11]

eTable 8. Sensitivity creatinine analyses

Characteristics	Balanced Solution	0.9% saline	Effect measure
	n= 5230	n= 5290	(95%CI)
Using creatinine criteria only (1)			
Creatinine > 2* reference creatinine at day 3	521/3668 (14.2%)	532/3695 (14.4%)	0.99 [0.86 - 1.13]
Creatinine > 2* reference creatinine or death at day 3	528/3668 (14.4%)	547/3695 (14.8%)	0.97 [0.85 - 1.11]
Creatinine > 2* reference creatinine at day 7	264/1460 (18.1%)	276/1520 (18.2%)	1.01 [0.84 - 1.22]
Creatinine > 2* reference creatinine or death at day 7	269/1460 (18.4%)	281/1520 (18.5%)	1.01 [0.84 - 1.22]
Only patients with previous creatinine measure (2)			
Incident renal failure* (using KDIGO ≥ 2) at day 3	463/2119 (21.8%)	470/2127 (22.1%)	0.98 [0.84 - 1.14]
KDIGO ≥ 2 or death at day 3	486/2119 (22.9%)	485/2127 (22.8%)	1.00 [0.87 - 1.16]
Incident renal failure* (using KDIGO ≥ 2) at day 7	112/2016 (5.6%)	130/2032 (6.4%)	0.87 [0.68 - 1.12]
KDIGO ≥ 7 or death at day 3	124/2016 (6.2%)	142/2032 (7%)	0.89 [0.70 - 1.13]
Using baseline creatinine value as reference (full data base) (3)			
Incident renal failure* (using KDIGO ≥ 2) at day	1048/3793 (27.6%)	1076/3834 (28.1%)	1.00 [0.90 - 1.11]
KDIGO ≥ 2 or death at day 3	1051/3793 (27.7%)	1087/3834 (28.4%)	0.99 [0.89 - 1.10]
Incident renal failure* (using KDIGO ≥ 2) at day 7	363/1533 (23.7%)	394/1593 (24.7%)	0.99 [0.83 - 1.17]
KDIGO ≥ 7 or death at day 3	365/1533 (23.8%)	396/1593 (24.9%)	0.99 [0.84 - 1.17]
All patients regardless of KDIGO at admission (4)			
Incident renal failure* (using KDIGO ≥ 2) at day	1224/3793 (32.3%)	1271/3834 (33.2%)	0.99 [0.88 - 1.11]
KDIGO ≥ 2 or death at day 3	1226/3793 (32.3%)	1280/3834 (33.4%)	0.97 [0.88 - 1.07]
Incident renal failure* (using KDIGO ≥ 2) at day 7	452/1533 (29.5%)	478/1593 (30%)	1.02 [0.87 - 1.19]
KDIGO ≥ 7 or death at day 3	454/1533 (29.6%)	480/1593 (30.1%)	1.02 [0.87 - 1.19]

eTable 9. Results for primary, secondary, and tertiary endpoints excluding patients with traumatic brain injury

Characteristics	Balanced solution	0.9% saline	Effect measure
	n= 5230	n= 5290	(95%CI)
Primary outcome			
90-day mortality (imputation)	1303/4981 (26.2%)	1389/5053 (27.5%)	0.96 [0.89 to 1.03]
Secondary outcomes			
Acute renal failure with need for renal replacement therapy within 90 days			
Incidence (per 1000 patient-day)	392/448.29 (0.87)	427/454.77 (0.94)	0.94 [0.82 - 1.08]
At day 1	26/4969 (0.5%)	29/5051 (0.6%)	
At day 2	111/4925 (2.3%)	130/5007 (2.6%)	
At day 3	173/4809 (3.6%)	205/4891 (4.2%)	
At day 7	256/4581 (5.6%)	302/4661 (6.5%)	
In hospital (at least one renal substitution in hospital stay)	372/4969 (7.5%)	409/5051 (8.1%)	0.79 [0.91 - 1.05]
Acute renal failure* (using KDIGO ≥ 2) at day 3	821/2938 (27.9%)	840/2928 (28.7%)	0.98 [0.87 - 1.10]
KDIGO ≥ 2 or death at day 3	822/2938 (28.0%)	846/2928 (28.9%)	0.97 [0.86 - 1.09]
Acute renal failure* (using KDIGO ≥ 2) at day 7	252/1037 (24.3%)	262/1053 (24.9%)	1.02 [0.84 - 1.25]
KDIGO ≥ 2 or death at day 7	254/1037 (24.5%)	263/1053 (25%)	1.03 [0.84 - 1.26]
Total SOFA score at day 3	4 [2 - 6] (n=3563)	3 [2 - 6] (n=3630)	0.08 [-0.03 - 0.19]
Cardiovascular SOFA > 2 at day 3	1221/3563 (34.3%)	1182/3630 (32.6%)	1.11 [1.00 - 1.23]
Neurological SOFA > 2 at day 3	517/3563 (14.5%)	520/3630 (14.3%)	1.02 [0.87 - 1.18]
Coagulation SOFA > 2 at day 3	161/3563 (4.5%)	159/3630 (4.4%)	1.04 [0.83 - 1.31]
Respiratory SOFA > 2 at day 3	240/3563 (6.7%)	237/3630 (6.5%)	1.03 [0.86 - 1.24]
Hepatic SOFA > 2 at day 3	44/3563 (1.2%)	48/3630 (1.3%)	0.97 [0.67 - 1.40]
Total SOFA score at day 7	4 [2 - 7] (n=1355)	4 [2 - 7] (n=1443)	0.26 [0.07 - 0.44]
Cardiovascular SOFA > 2 at day 7	386/1355 (28.5%)	381/1443 (26.4%)	1.16 [0.98 - 1.37]
Neurological SOFA > 2 at day 7	383/1355 (28.3%)	328/1443 (22.7%)	1.39 [1.16 - 1.67]
Coagulation SOFA > 2 at day 7	61/1355 (4.5%)	68/1443 (4.7%)	1.04 [0.75 - 1.45]
Respiratory SOFA > 2 at day 7	139/1355 (10.3%)	137/1443 (9.5%)	1.13 [0.88 - 1.44]
Hepatic SOFA > 2 at day 7	24/1355 (1.8%)	26/1443 (1.8%)	1.06 [0.68 - 1.65]
Mechanical ventilation-free days within 28 days	27 [19 - 28] (n=4968)	27 [18 - 28] (n=5051)	0.10 [-0.17 - 0.39]
Tertiary outcomes			
Death in ICU	853/4969 (17.2%)	889/5051 (17.6%)	0.99 [0.88 - 1.11]
Death in hospital	1102/4969 (22.2%)	1175/5051 (23.3%)	0.94 [0.85 - 1.05]
ICU length of stay (days)	3 [2 - 7] (n=4969)	3 [2 - 7] (n=5051)	0.99 [0.94 - 1.04]
Length of stay (days)	8 [5 - 17] (n=4969)	8 [5 - 17] (n=5051)	0.98 [0.93 - 1.03]