Supplemental Online Content

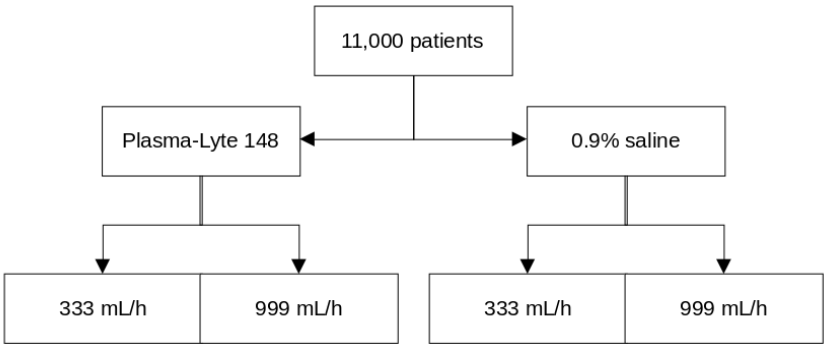
Zampieri FG, Machado FR, Biondi RS, et al; for the BaSICS investigators and the BRICNet members. Effect of slower vs faster intravenous fluid bolus rates on mortality in critically ill patients: the BaSICS randomized clinical trial. *JAMA*. Published online August 10, 2021. doi:10.1001/jama.2021.11444

eMethods

Additional Trial Procedures Information

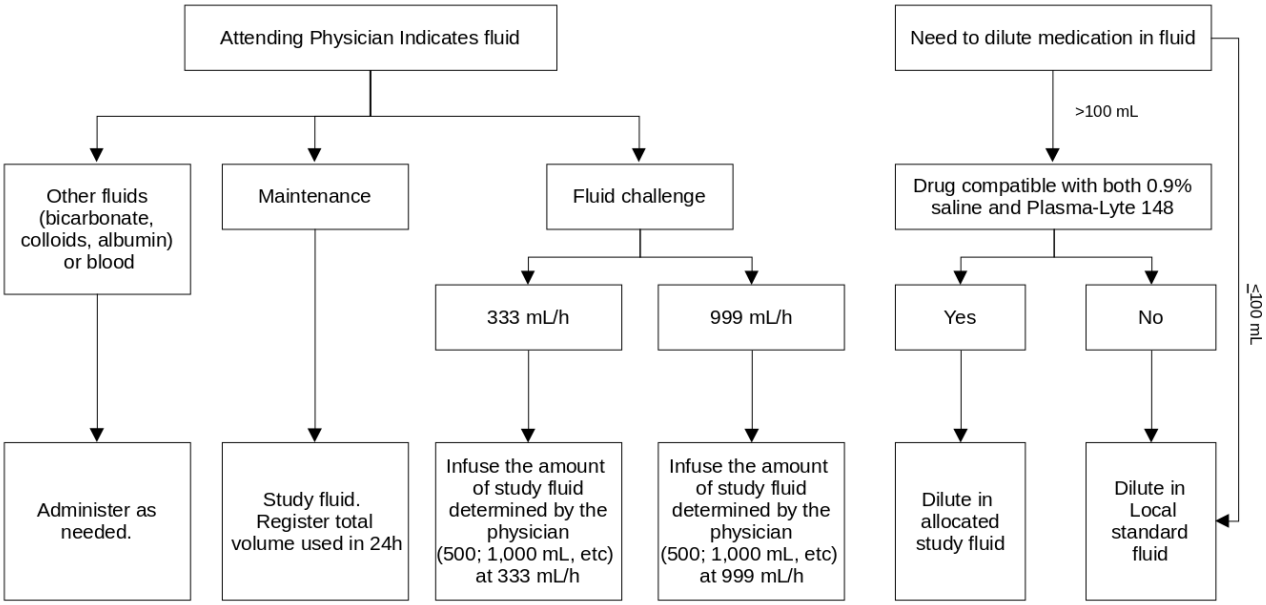
Overview of BaSICS trial: BaSICS was a large factorial trial. Patients were randomized to two different intervention arms. The first was the comparison between Plasma-Lyte 148 versus 0.9% saline as preferred fluid for resuscitation, maintenance, and dilutions in critically ill patients. The second arm compared two –different infusion rates (333 mL/h – "slower" versus "control" 999 mL/h). The randomization scheme is shown in the figure below:

eFigure 1 – Study scheme



Fluids were labeled A, B, C… F. Therefore, a given patient could be randomized to B-slower, meaning we should receive "B" labeled fluids as discussed below and, in case of need for fluid challenge, a rate 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, following the scheme below:

eFigure 2 – Fluid management in BaSICS



Protocol for fluid challenge: Fluid challenges were performed at the discretion of the attending physician. The attending physician could define the volume of fluid challenge, but rate was set according to randomization arm. We required that fluids be infused through an infusion pump with rate set at the assigned group (333 or 999 mL/h). We allowed faster infusion rates in the slower infusion group if patients had active bleeding demanding fluid resuscitation or had very severe hypotension (systolic blood pressure below 80 mmHg or mean arterial pressure below 50 mmHg).

Screening log: BaSICS was a large trial, and a screening log was not possible.

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 (urinary output was collected on a daily basis). 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.

Mechanical Ventilation Free-days: Mechanical ventilation free days was defined as sum of calendar days the patient did not use mechanical ventilation up to 28-days. We assigned zero to patients that required mechanical ventilation at any time in the ICU and that died during hospital-stay regardless of the duration

Missing values and imputation

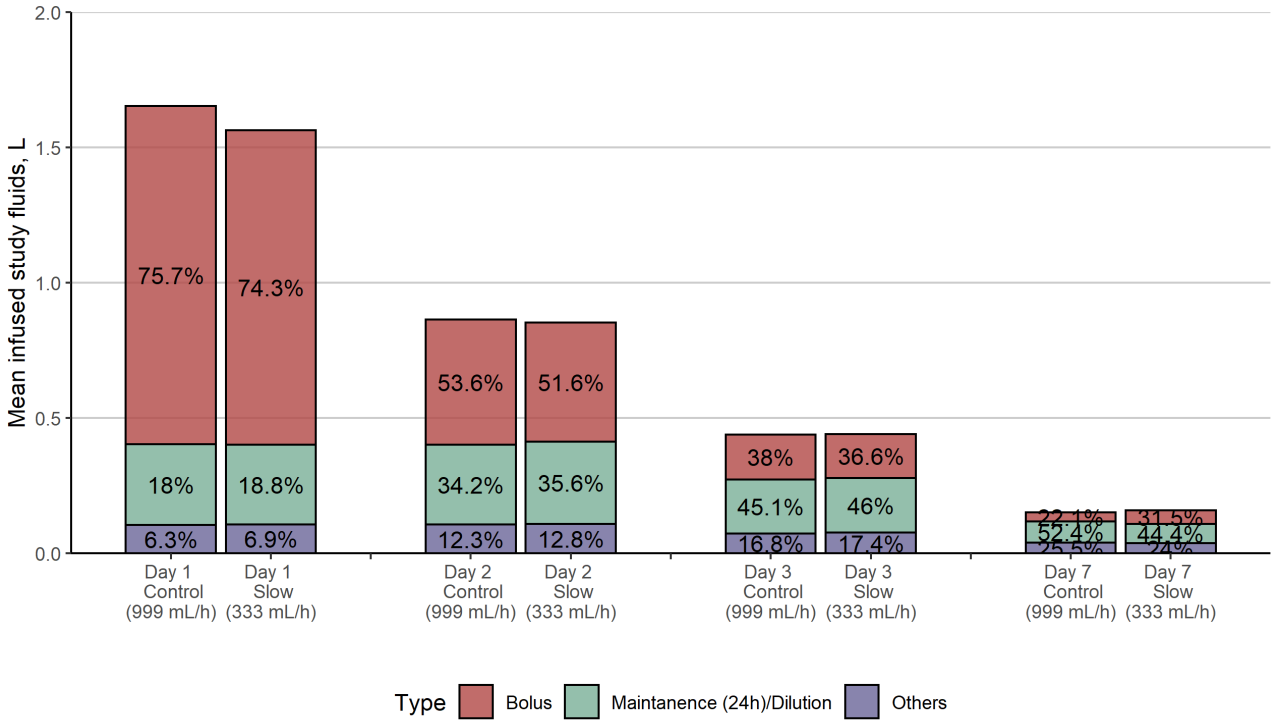
The following variables had missing values that were imputed for Table 1:

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 patient's 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 (surgical, non-surgical with or without sepsis): There were 28 missing values. These values were imputed.
13. 90-day mortality: There were 15 missing values that were imputed.

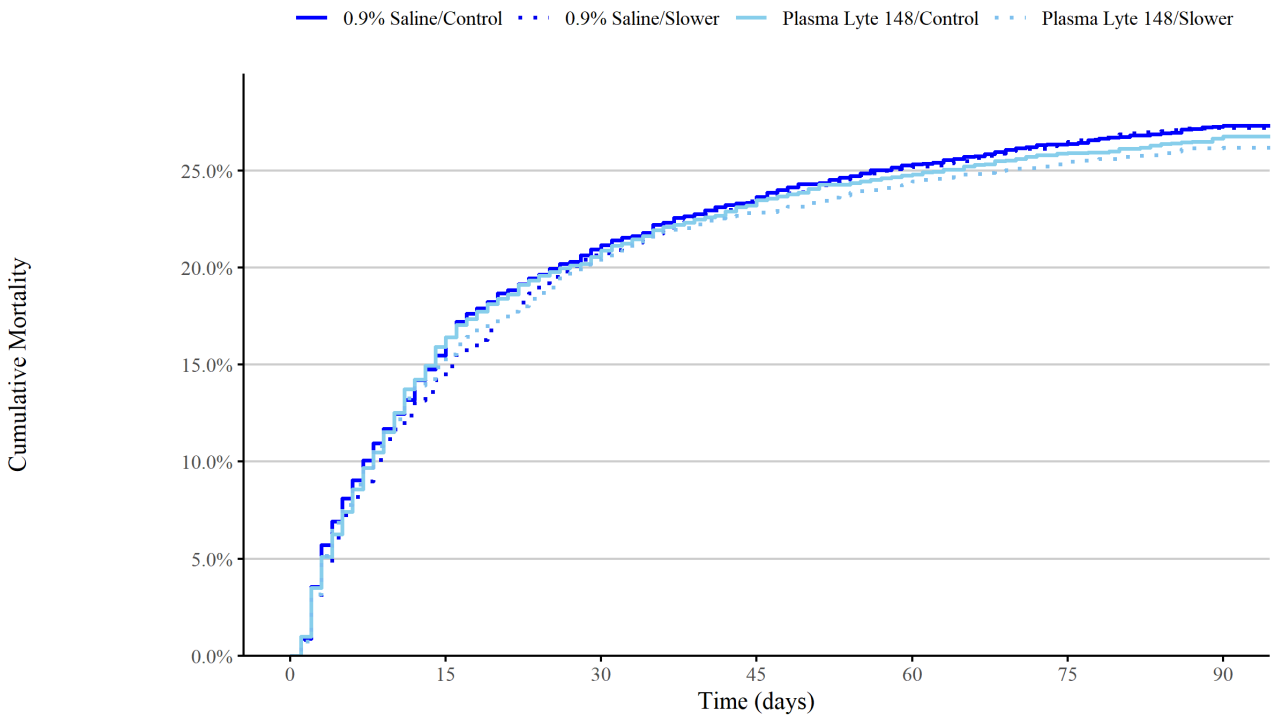
Imputation procedures: Imputation was made in a single model in {mice} using age, sex, enrolling site, randomization creatinine, SOFA, admission type, use of fluid in the 24 hours before enrollment, presence of heart failure or cirrhosis, traumatic brain injury at enrollment, hypotension at enrollment, 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/.

eFigure 3 – Proportion of fluids used at days 1, 3 and 7 as bolus at assigned (333 versus 999 mL/h), maintenance and dilutions or other rates



eFigure 4 – Primary outcome results according to both interventions in BaSICS (infusion rate and fluid type). P value for interaction 0.98



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
Plasma Lyte 148/Control	2603	2182	2060	1991	1951	1920	1899
Plasma Lyte 148/Slower	2627	2225	2079	2013	1971	1943	1922

eTable 1 - Baseline characteristics of the included patients of the four groups of the trial

Characteristics	Plasma Lyte / Slower infusion rate	Plasma Lyte / Control infusion rate	0.9% sodium chloride/ Slower 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 (n=2603)	61 ± 17 (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	1262/2627 (48%)	1238/2603 (47.6%)	1317/2649 (49.7%)	1275/2641 (48.3%)
Unplanned admissions	1365/2627 (52%)	1365/2603 (52.4%)	1332/2649 (50.3%)	1366/2641 (51.7%)
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%)	260/2596 (10%)	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=2627)	12 [8 - 17] (n=2603)	12 [8 - 17] (n=2649)	12 [8 - 17] (n=2641)
SOFA score - median (IQR)	4 [2 - 6] (n=2627)	4 [2 - 7] (n=2603)	4 [2 - 7] (n=2649)	4 [2 - 7] (n=2641)
KDIGO criteria for acute kidney injury > = 1	822/2627 (31.3%)	872/2603 (33.5%)	887/2649 (33.5%)	893/2641 (33.8%)
Sepsis	470/2627 (17.9%)	500/2603 (19.2%)	498/2649 (18.8%)	520/2641 (19.7%)
Traumatic brain injury	132/2627 (5%)	117/2603 (4.5%)	120/2649 (4.5%)	116/2641 (4.4%)
Hypotension (MAP < 65 or systolic arterial pressure < 90 or use of vasopressors) - no. (%)	1580/2627 (60.1%)	1591/2603 (61.1%)	1586/2649 (59.9%)	1616/2641 (61.2%)
Mechanical ventilation - no./total no. (%)				
Non-invasive mechanical ventilation >12h	368/5276 (7%)	306/5244 (5.8%)	368/5276 (7%)	306/5244 (5.8%)
Invasive mechanical ventilation	2304/5276 (43.7%)	2357/5244 (44.9%)	2304/5276 (43.7%)	2357/5244 (44.9%)
Serum creatinine - mg/dL (mean (SD))	1.2 ± 0.9 (n=5276)	1.2 ± 0.9 (n=5244)	1.2 ± 0.9 (n=5276)	1.2 ± 0.9 (n=5244)
Creatinine ≤ 1.5 mg/dL	4223/5276 (80.0%)	4144/5244 (79.0%)	4223/5276 (80.0%)	4144/5244 (79.0%)
Creatinine 1.5-2.5	709/5276 (13.4%)	746/5244 (14.2%)	709/5276 (13.4%)	746/5244 (14.2%)
Creatinine > 2.5	344/5276 (6.6%)	354/5244 (6.8%)	344/5276 (6.6%)	354/5244 (6.8%)
Cirrhosis or acute liver failure	117/5276 (2.2%)	150/5244 (2.9%)	117/5276 (2.2%)	150/5244 (2.9%)
Heart failure	544/5276 (10.3%)	596/5244 (11.4%)	544/5276 (10.3%)	596/5244 (11.4%)

Characteristics	Plasma Lyte / Slower infusion rate	Plasma Lyte / Control infusion rate	0.9% sodium chloride/ Slower infusion rate	0.9% sodium chloride / Control infusion rate
	n = 2627	n = 2603	n = 2649	n = 2641
Time from ICU admission to randomization - days, median [percentiles 2.5% - 97.5%]	0 [0 - 1] (n=5276)	0 [0 - 1] (n=5244)	0 [0 - 1] (n=5276)	0 [0 - 1] (n=5244)
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%)	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%)	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%)	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%)	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 infusion rate according to day of assessment

Adherence	Slower Infusion Rate	Control Infusion Rate
	n = 5276	**n = 5244**
Day 1		
Patients with at least one bolus infused for expansion	5,079/5,237 (97%)	5,075/5,206 (97.5%)
All fluid challenges at the allocated rate	4,907/5079 (96.6%)	5,046/5,075 (99.4%)
Day 2		
Patients with at least one bolus infused for expansion	2,398/3871 (61.9%)	2,338/3,824 (61.1%)
All fluid challenges at the allocated rate	2,350/2398 (98%)	2,326/2,338 (99.5%)
Day 3		
Patients with at least one bolus infused for expansion	1,121/2472 (45.3%)	1,129/2,484 (45.5%)
All fluid challenges at the allocated rate	1,104/1121 (98.5%)	1,125/1,129 (99.6%)
Day 7		
Patients with at least one bolus infused for expansion	383/964 (39.7%)	282/918 (30.7%)
All fluid challenges at the allocated rate	377/383 (98.4%)	281/282 (99.6%)

eTable 3 – Volume of fluid infused at Days 1, 2, 3, and 7

Mean (SD) study's fluid volume	Slower Infusion Rate (n = 5276)	Control Infusion Rate (n = 5244)
Day 1		
Bolus	1,162 (916)	1,252 (1,009)
Maintenance (24h)/Dilution	294 (685)	298 (584)
Other rates	107 (315)	105 (313)
Day 2		
Bolus	440 (743)	463 (1176)
Maintenance (24h)/Dilution	304 (678)	295 (605)
Other rates	109 (329)	106 (337)
Day 3		
Bolus	161 (480)	167 (483)
Maintenance (24h)/Dilution	202 (549)	199 (536)
Other rates	77 (299)	74 (290)
Day 7		
Bolus	50 (296)	33 (200)
Maintenance (24h)/Dilution	71 (328)	79 (368)
Others rates	38 (207)	39 (216)

eTable 4 – Primary outcome model

Coefficient	Estimative	Standard error	HR [95%CI]	p value
Plasma-Lyte 148 group	-0.02	0.05	0.98 [0.88 to 1.08]	0.64
Slower infusion (333 mL/h)	*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	2.8 [2.53 to 3.1]	<0.01
Unplanned admission with sepsis	1.22	0.06	3.4 [3.04 to 3.8]	<0.01
Interaction (Plasma Lyte 148:Slower infusion)	0	0.08	1 [0.86 to 1.16]	0.98

eTable 5 – Subgroup results

Subgroup	Slower Infusion Rate	Control Infusion Rate	HR [IC95%]
	N = 5,276	**N = 5,244**	
All patients	1,406/5,276 (26.6%)	1,414/5,244 (27%)	1.03 [0.96 to 1.11]
KDIGO			
≤ 1	988/4,390 (22.5%)	996/4,320 (23.1%)	1 [0.92 to 1.1]
≥ 2	418/886 (47.2%)	418/924 (45.2%)	1.09 [0.95 to 1.25]
Sepsis			
No	935/4,309 (21.7%)	934/4,224 (22.1%)	1 [0.92 to 1.1]
Yes	471/967 (48.7%)	480/1,020 (47.1%)	1.07 [0.94 to 1.22]
Traumatic brain injury			
No	1341/5,022 (26.7%)	1,351/5,012 (27%)	1.03 [0.96 to 1.11]
Yes	65/254 (25.6%)	63/232 (27.2%)	1.01 [0.71 to 1.43]
Surgical patients			
No	887/2,050 (43.3%)	884/2,074 (42.6%)	1.04 [0.95 to 1.15]
Yes	519/3,226 (16.1%)	530/3,170 (16.7%)	1 [0.89 to 1.13]
APACHE II			
< 25	1153/4,896 (23.5%)	1,148/4,855 (23.6%)	1.03 [0.95 to 1.12]
≥ 25	253/380 (66.6%)	266/389 (68.4%)	0.98 [0.82 to 1.17]
Saline use 24h before randomization			
< 1.0 L	1,206/4,281 (28.2%)	1204/4,282 (28.1%)	1.05 [0.97 to 1.14]
≥ 1.0 L	190/978 (19.4%)	206/951 (21.7%)	0.89 [0.73 to 1.09]

* sum does not reach total sample size because missing information was not imputed (28 missing data).

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.

eTable 6 – Primary outcome for complete case analyses

Slower Infusion Rate	Control Infusion Rate	Hazard Ratio [95% CI]	P value
1400/5267 (26.6%)	1412/5238 (27%)	1.02 [0.95 to 1.1]	0.53

B. Primary endpoint results in according to baseline heart failure diagnosis:

eTable 7 – Primary outcome for patients with known heart failure status at enrollment

Heart Failure	**Slower Infusion Rate (333 mL/h)**	**Control Infusion Rate (999 mL/h)**	**Hazard Ratio [95% CI]**	**P value**
No	1278/4732 (27%)	1281/4648 (27.6%)	1.02 [0.94 to 1.1]	0.65
Yes, with unknown EF*	45/124 (36.3%)	56/134 (41.8%)	1.02 [0.68 to 1.52]	0.92
EF > 50%	15/87 (17.2%)	16/92 (17.4%)	0.82 [0.39 to 1.73]	0.61
EF ≤ 50%	68/333 (20.4%)	61/370 (16.5%)	1.3 [0.92 to 1.85]	0.14

EF = Ejection Fraction

C. Hemodynamic SOFA at days 3 and 7 according to fluid type used

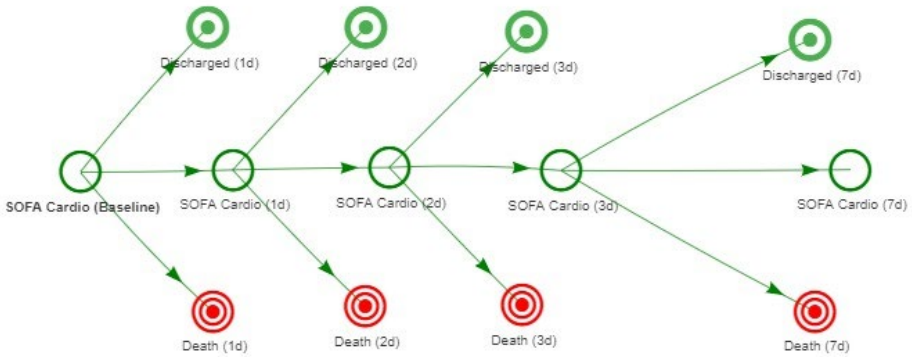
eTable 8 – Hemodynamic SOFA at days 3 and 7 according to infusion rate and fluid type

Interactions	**Slower Infusion Rate (333 mL/h)**	**Control Infusion Rate (999 mL/h)**	**OR [IC95%]**	**P value**
	n = 5276	**n = 5244**		
Hemodynamic SOFA > 2 at day 3				
Plasma Lyte-148	644/1922 (33.5%)	675/1867 (36.2%)	0.90 [0.78 - 1.04]	0.144
0.9% Saline	608/1925 (31.6%)	663/1921 (34.5%)	0.88 [0.76 - 1.01]	0.069
Hemodynamic SOFA > 2 at day 7				
Plasma Lyte-148	207/791 (26.2%)	213/740 (28.8%)	0.90 [0.71 - 1.13]	0.348
0.9% Saline	196/809 (24.2%)	213/785 (27.1%)	0.86 [0.69 - 1.08]	0.207

D. Bayesian Network for Analysis of important competing events

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. Our focus was hemodynamic profile based on cardiovascular SOFA score. The network defined was:

eFigure 5 – Bayesian Network



Therefore, from baseline hemodynamic SOFA score, patients transitioned to death, discharge or to the next measurement point (days 1, 2, 3 and 7). We can query the network and obtain conditional probabilities, for example: What is the probability that patients in slower infusion group were not using vasopressors at day 3 given they were not discharged and were alive in the ICU until that day. The same query can be made for patients in control rate. The probability estimates can be used to calculate relative risks (ratio of probabilities), odds ratios (ratio of odds, defined as [probability/(1-probability)]), etc. This analysis can therefore accommodate competing events (early discharge and death). We queried the Bayesian network for some relevant hemodynamic questions and extracted probabilities and odds ratios, as shown below. Results are provided as median (95% credible interval – CrI).

In brief, we could detect small differences in probabilities that patients were either discharged alive from the ICU or were not using vasopressors at day 3 for slower versus control infusion. Differences were, however, exceedingly small (close to 2 or 3%).

eTable 9 – Results for Bayesian network queries

Query	Probability for Slower Group (95% CrI)	Probability for Control Group (95% CrI)	Odds Ratio (slower versus control) 95% CrI
Patient without vasopressor or discharged at day 1 given baseline cardiovascular SOFA 0, 1, or 2	0.75 [0.74 - 0.77]	0.76 [0.74 - 0.77]	0.98 [0.87 - 1.10]
Patient without vasopressor or discharged at days 1 or 2 given baseline cardiovascular SOFA 0, 1, or 2	0.67 [0.66 - 0.69]	0.67 [0.66 - 0.69]	1.00 [0.90 - 1.12]
Patient without vasopressor or discharged at days 1, 2 or 3 given baseline cardiovascular SOFA 0, 1, or 2	0.63 [0.62 - 0.65]	0.63 [0.61 - 0.65]	1.02 [0.92 - 1.14]
Patient without vasopressor or discharged at days 1, 2, 3, or 7 given baseline cardiovascular SOFA 0, 1, or 2	0.57 [0.55 - 0.59]	0.57 [0.55 - 0.59]	1.01 [0.91 - 1.12]
Patient without vasopressor or discharged at days 3 given baseline cardiovascular SOFA 0, 1, or 2	0.81 [0.80 - 0.82]	0.79 [0.78 - 0.81]	1.10 [0.98 - 1.22]
Patient without vasopressor or discharged at day 3 regardless of baseline cardiovascular SOFA	0.71 [0.70 - 0.73]	0.69 [0.68 - 0.71]	**1.11 [1.01 - 1.21]**
Patient without vasopressor or discharged at day 1 given baseline cardiovascular SOFA 3 or 4	0.09 [0.07 - 0.10]	0.10 [0.09 - 0.11]	0.84 [0.68 - 1.04]
Patient without vasopressor or discharged at day 2 given baseline cardiovascular SOFA 3 or 4	0.30 [0.28 - 0.32]	0.30 [0.28 - 0.32]	1. 00 [0.88 - 1.12]
Patient without vasopressor or discharged at day 3 given baseline cardiovascular SOFA 3 or 4	0.56 [0.54 - 0.58]	0.53 [0.51 - 0.55]	**1.14 [1.03 - 1.27]**