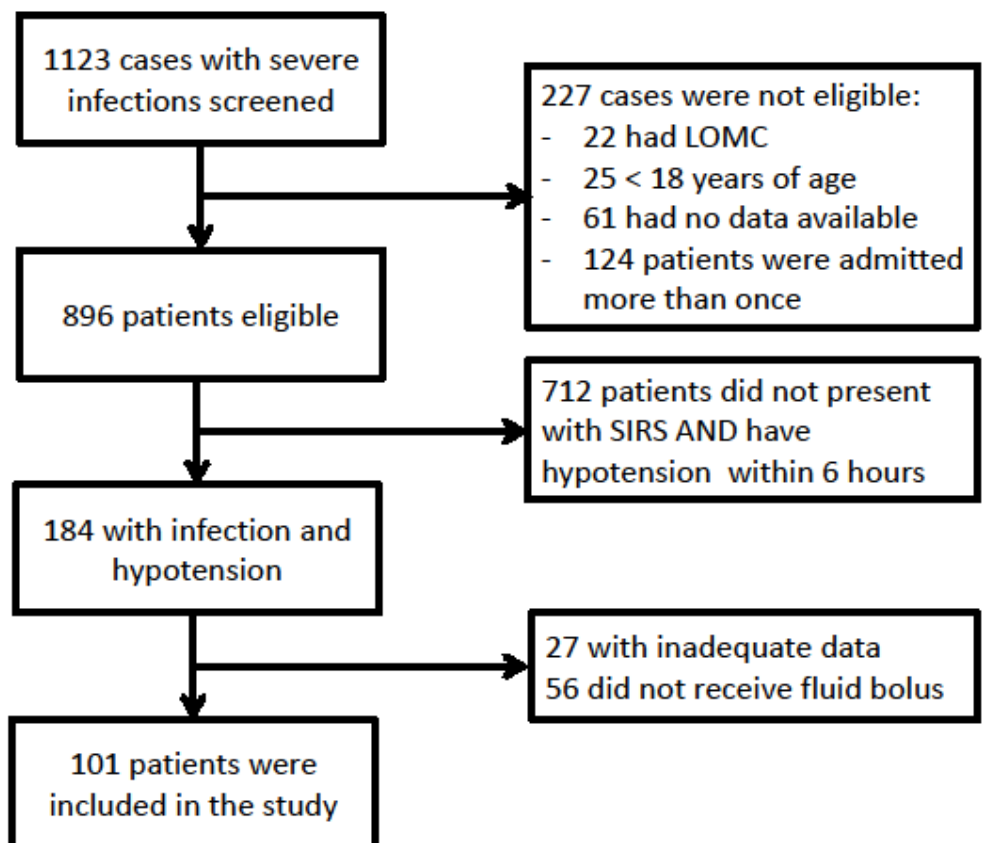


This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Appendix. Supplementary figures and tables

Figure A1. Flowchart describing patient selection process



LOMC Limitations in medical care

In case of several admissions for the same patient the first chronologically was used

Bolus was defined as fluid administration $> 250 \text{ mls} \times \text{h}^{-1}$

Figure A2. Changes in MAP with different fluid bolus volume in the whole cohort. A positive value on the Y-axis indicates a rise in blood pressure

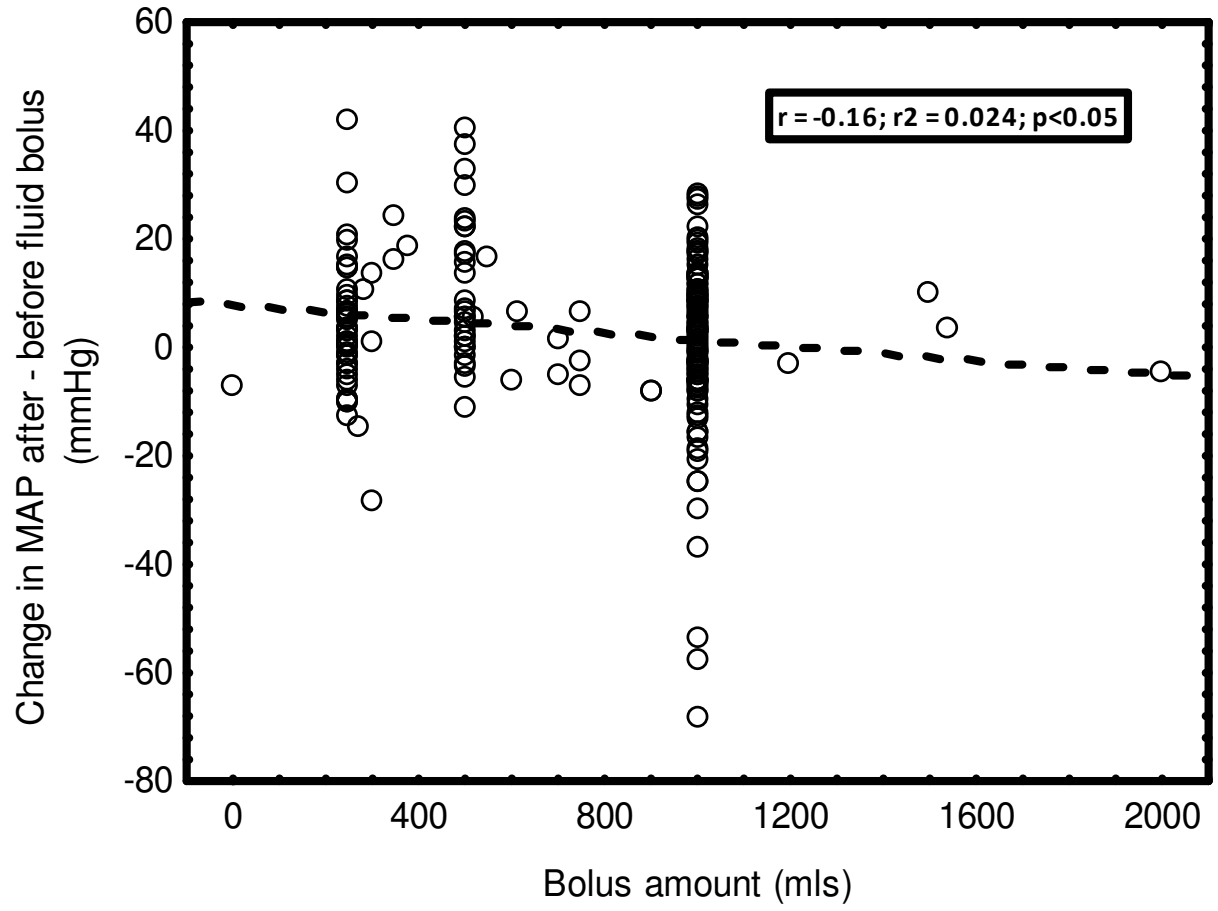


Figure A3. Changes in MAP with different fluid bolus volume in patients that were hypotensive or severely hypotensive on arrival to the ED. A positive value indicates a rise in blood pressure

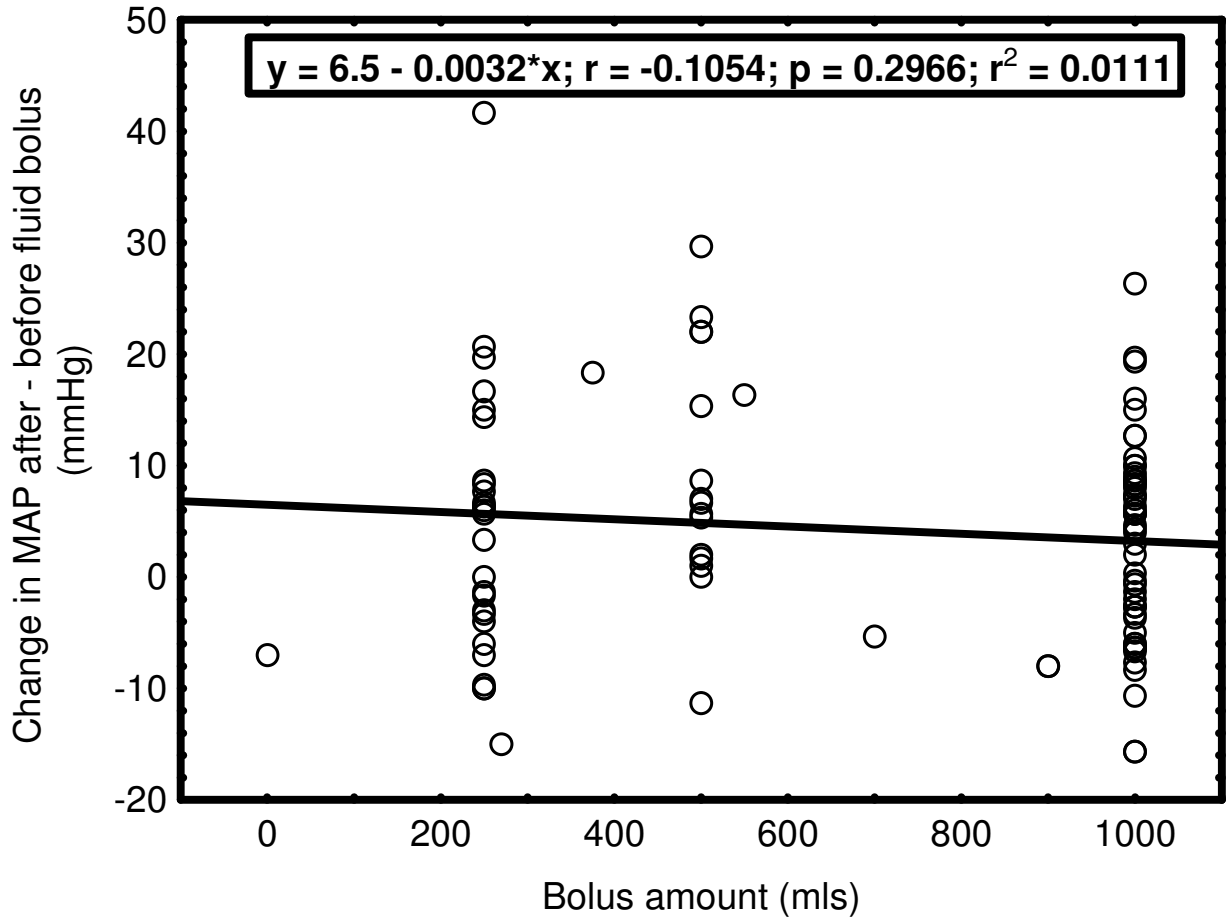


Figure A4. Changes in mean arterial pressure (MAP) in patients treated with noradrenaline (NA) on arrival to the ED, prior and after the commencement of the NA infusion. The MAP increased after the start of the NA infusion ($p > 0.01$).

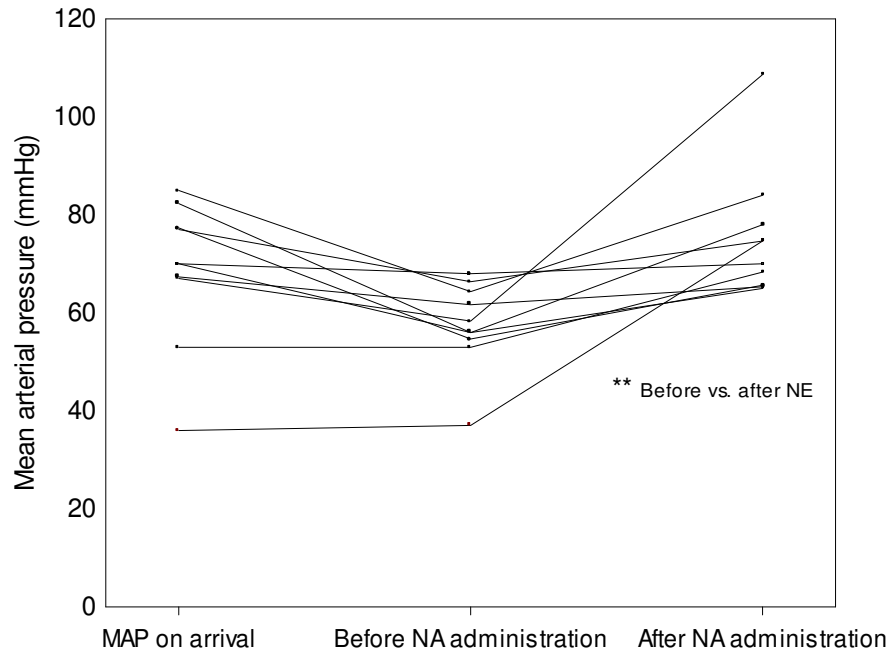


Figure A5. Changes in systolic arterial pressure (SAP) in patients who were hypotensive (H) on arrival (SBP < 100 mmHg; H); patients who were severely hypotensive (S) on arrival (SBP < 90 mmHg; S); patients who became hypotensive (NH) and patients who became severely hypotensive (NS) during the first six hours after arrival to the emergency department. Changes are depicted in a box plot. Box: mean \pm SE; whisker: mean \pm 0.95 confidence interval

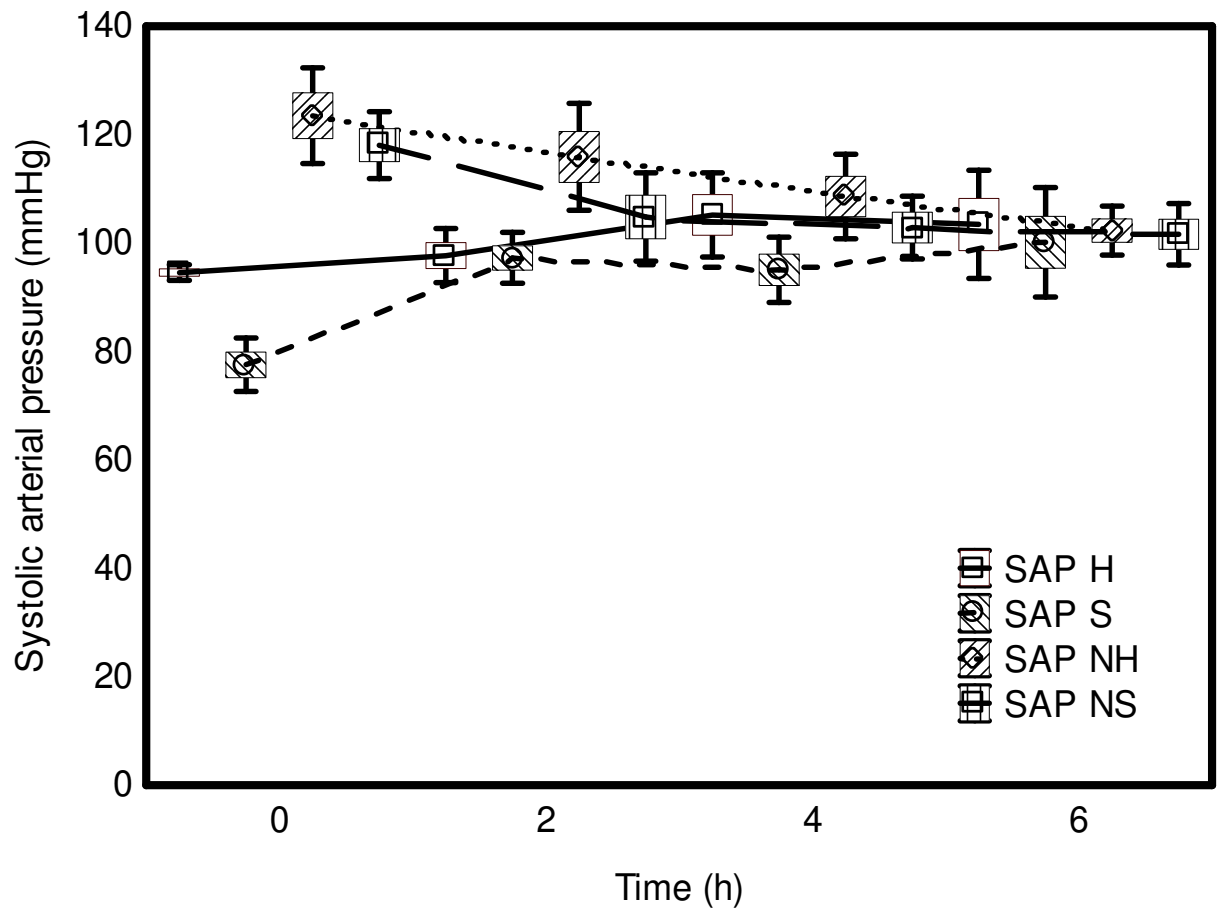


Figure A6. Scatterplot of the total fluid administered during the first six hours after arrival to the emergency department and the change in mean arterial pressure during the same period in severely hypotensive patients. A positive value on the Y-axis indicates a rise in blood pressure

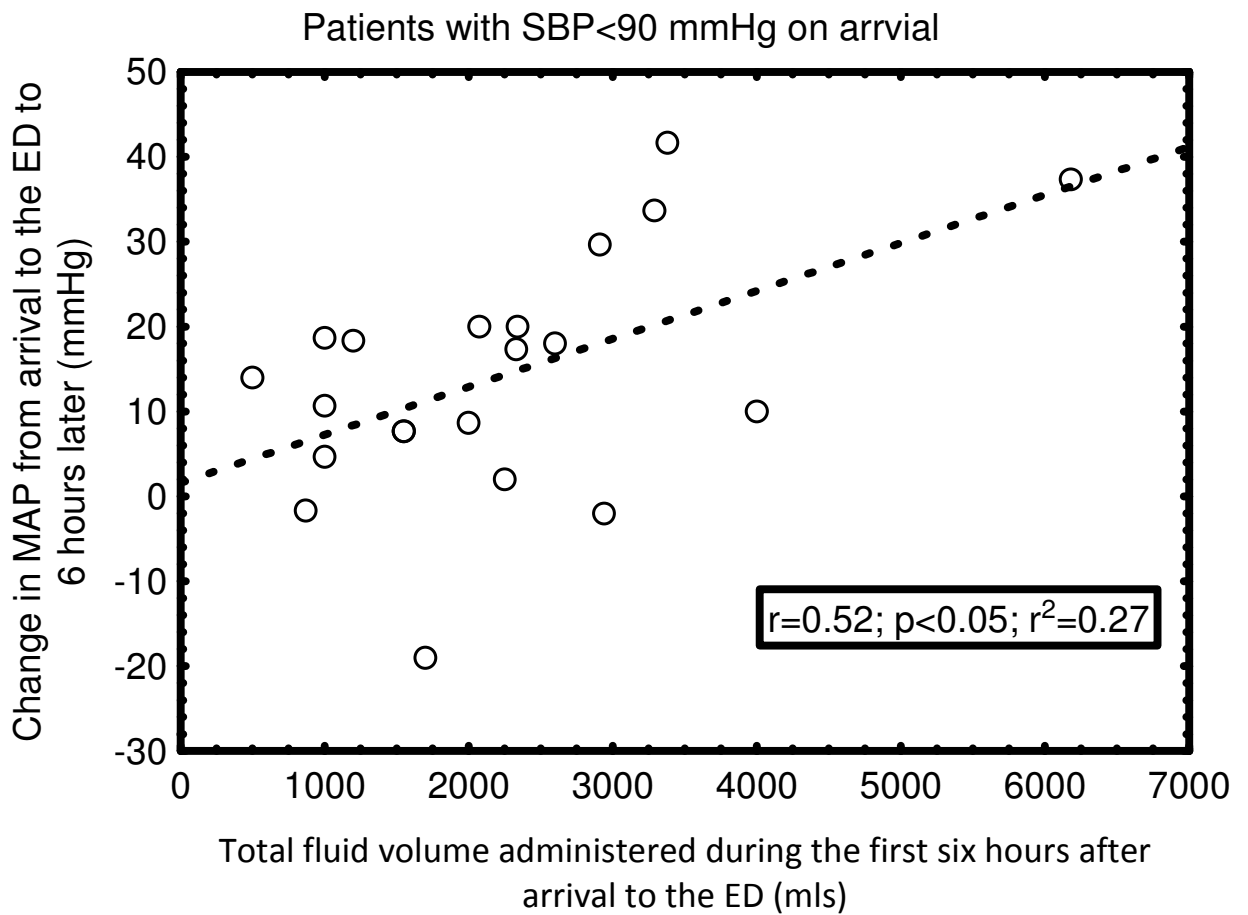


Table A1. Characteristics of full study cohort and patients receiving fluid bolus therapy

All ED patients screened		
<u>Diagnosis and diagnosis codes</u>	Number of cases scanned	Number of patients included
Gastroenteritis and colitis of unspecified origin (A09.9)	30	3
Perforation of oesophagus (K22.3)	2	0
Urinary tract infection (N39.0)	253	8
Acute abdomen (R10.0)	9	0
Bronchopneumonia, unspecified (J18.0)	12	1
Lobar pneumonia, unspecified (J18.1)	9	1
Acute bronchitis, unspecified (J20.9)	4	0
Acute bronchitis, unspecified (J22)	326	14
Pneumonitis due to food and vomit (J69.0)	148	8
Other specified sepsis (A41.8)	26	10
Sepsis, unspecified (A41.9)	300	54
Bacterial infection, unspecified (A49.9)	8	2
Fluid bolus treated patients		
<u>Co-morbidities</u>	No. of observations (in 101 cases)	
Heart failure	17	
Coronary artery disease	17	
CODP	15	
Diabetes mellitus	12	
HIV	0	
Hypertension	34	
Liver failure	8	
History of malignancy	20	
Neurological disease	23	
History of smoking	35	
<u>Sepsis details</u>	50	
Urinary sepsis	12	
Peritonitis	2	
Other intra-abdominal processes	15	
Abscess in extremities	2	
Other causes of sepsis	22	
Severe sepsis	75	
Septic shock	36	
Positive blood culture	18	
Antibiotics given within 6 hours from arrival in the emergency department	83	

Table A2. Vital signs in different subgroups. Hypotensive patients vs. severely hypotensive patients during the first 6 hours

	Hypotensive patients n=25				Severely hypotensive patients n=21			
	On arrival	2 hours	4 hours	6 hours	On arrival	2 hours	4 hours	6 hours
Crystalloids administered (ml)		500(0-5000)	580(0-1720)	500(0-2000)		785(0-5000)	480(0-1460)	490(0-1350)
Colloids administered (ml)		0(0-0)	340(0-750)	460(0-700)		0(0-500)	0(0-750)	0(0-600)
Packed red cells administered (ml)		0(0-0)	00(0-0)	50(0-150)		0(0-0)	0(0-0)	0(0-150)
Fresh frozen plasma administered (ml)		0(0-0)	00(0-0)	30(0-180)		0(0-0)	0(0-0)	0(0-180)
Platelets administered (ml)		0(0-0)	0(0-750)	0(0-700)		0(0-0)	0(0-0)	0(0-0)
Fraction of inspired O ₂	0.21(0.21-0.28)	0.21(0.21-0.32)	0.21(0.21-0.32)	0.21(0.21-0.32)	0.21(0.21-0.28)	0.21(0.21-0.28)	0.30(0.21-0.34)	0.28(0.21-0.32)
Body temperature (°C)	37.4±1.4	37.0±1.4	36.7±1.2	36.8±1.2*	37.1±1.4	36.5±1.2	36.3±1.2	36.3±1.4
Heart rate (x min ⁻¹)	103±25	93±23	90±19	88±21	104±27	97±26	96±21	92±20
Systolic blood pressure (mm Hg)	106±23***	105±17	104±15*	103±17	78±11	97±10	95±13	100±21
Diastolic blood pressure (mm Hg)	65±14***	61±10*	59±12	59±15*	45±8	53±8	53±11	54±12
Mean arterial pressure (mmHg)	71±5***	73±10*	75±16*	76±17	56±8	68±8	66±9	70±14
Respiratory rate (x min ⁻¹)	18(16-23)	18(16-22)	18(16-22)	18(16-22)	18(16-20)	19(18-22)	18(16-20)	18(18-20)
Arterial SaO ₂	97(94-99)	98(97-100)	98(96-100)	98(97-100)	97(94-99)	99(97-100)	99(97-100)	98(97-100)
Arterial pH	7.37±0.08	7.36±0.08	7.39±0.09	7.40±0.07	7.32±0.09	7.35±0.08	7.41±0.09	7.35±0.06
Arterial PaO ₂ (mm Hg)	87±66	151±135	122±76	113±42	32±11	53±35	115±87	112±36
Arterial PaCO ₂ (mm Hg)	42±11	40±13	37±4	37±6	42±10	39±9	37±2	40±6
Plasma base excess (mmol x l ⁻¹)	-1.6±4.6	-2.6±5.5	-1.6±5.4	-1.4±3.7	-4.3±5.7	-3.6±5.4	-0.4±6.2	-2.5±4.8
Plasma lactate (mmol x litre ⁻¹)	2.0(1.2-2.4)	2.1(1.5-3.1)	2.2(1.9-3.2)	1.8(1.4-2.3)	2.3(1.5-3.0)	1.8(1.5-3.0)	2.8(2.1-2.8)	2.0(1.6-2.8)
Blood haemoglobin (g x l ⁻¹)	124±24	122±22	113±22	120±20	115±28	118±22	96±26	123±18
Plasma chloride (mmol x l ⁻¹)	101±5	102±6	102±7	103±6	100±5	102±4	98±6	104±3
Plasma	129(71-	140(72-	123(90-	75(57-94)	142(85-	161(131-	20(20-20)	90(77-

creatinine ($\mu\text{mol} \times \text{l}^{-1}$)	149)	160)*	150)		216)	182)		103)
Plasma Albumin (g x l^{-1})	33 \pm 6	32 \pm 7	31 \pm 5	26 \pm 11	30 \pm 8	28 \pm 6	-	-

^R Range * $p < 0.05$ *** $p < 0.001$

Table A3. Vital signs in different subgroups. Survivors vs. non-survivors patients during the first 6 hours

	Survivors at 28 days n=75				Non- survivors at 28 days n=26			
	On arrival	2 hours	4 hours	6 hours	On arrival	2 hours	4 hours	6 hours
Crystalloids administered (ml)		500(0-5000) ^R	580(0-1720) ^R	500(0-2000) ^R		500(0-1750) ^R	500(0-1500) ^R	400(0-2500) ^R
Colloids administered (ml)		0(0-0) ^R	0(0-750) ^R	0(0-700) ^R		0(0-500) ^R	0(0-620) ^R	0(0-500) ^R
Packed red cells administered (ml)		0(0-0) ^R	0(0-0) ^R	0(0-150) ^R		0(0-0) ^R	0(0-0) ^R	0(0-150) ^R
Fresh frozen plasma administered (ml)		0(0-0) ^R	0(0-0) ^R	0(0-180) ^R		0(0-0) ^R	0(0-0) ^R	0(0-300) ^R
Platelets administered (ml)		0(0-0) ^R	0(0-0) ^R	0(0-200) ^R		0(0-0) ^R	0(0-0) ^R	0(0-0) ^R
Fraction of inspired O ₂	0.21(0.21-0.28)	0.21(0.21-0.32)**	0.21(0.21-0.32)**	0.21(0.21-0.32)	0.28(0.21-0.50)	0.28(0.21-0.44)	0.32(0.21-0.50)	0.32(0.21-0.48)
Body temperature (°C)	37.4±1.4	37.0±1.4	36.7±1.2	36.8±1.2**	37.2±1.4	36.4±1.2	36.5±1.1	36.1±0.6
Heart rate (x min ⁻¹)	103±25*	93±23*	90±19**	88±21***	118±31	108±28	104±22	102±21
Systolic blood pressure (mm Hg)	106±23	105±17	104±15	103±17	99±21	102±25	100±20	99±20
Diastolic blood pressure (mm Hg)	65±14**	61±10	59±12**	59±15	55±16	57±15	53±16	56±13
Mean arterial pressure (mmHg)	78±16*	76±11	74±11**	74±14	69±17	73±14	68±15	71±11
Respiratory rate (x min ⁻¹)	18(16-23)**	18(16-22)***	18(16-22)**	18(16-22)	23(20-28)	24(19-28)	20(19-25)	19(18-23)
Arterial SaO ₂	97(94-99)	98(97-100)*	98(96-100)	98(97-100)*	97(94-99)	97(95-99)	97(96-99)	97(96-98)
Arterial pH	7.37±0.08	7.36±0.08	7.39±0.09	7.40±0.07	7.33±0.13	7.29±0.13	7.30±0.12	7.29±0.17
Arterial PaO ₂ (mm Hg)	87±66	151±135	122±76	113±42	73±77	47±15	102±67	107±68
Arterial PaCO ₂ (mm Hg)	42±11	40±13*	37±4	37±6*	47±18	53±22	49±13	48±19
Plasma base excess (mmol x l ⁻¹)	-1.6±4.6	-2.6±5.5	-1.6±5.4	-1.4±3.7	-3.1±6.1	-3.4±6.0	-3.5±6.0	-4.8±6.3
Plasma lactate (mmol x litre ⁻¹)	2.0(1.2-2.4)	2.1(1.5-3.1)	2.2(1.9-3.2)	1.8(1.4-2.3)	2.0(1.4-2.9)	1.8(1.5-3.6)	3.5(2.3-7.0)	2.4(1.5-4.7)
Blood haemoglobin (g x l ⁻¹)	124±24	122±22	113±22	120±20	119±23	121±24	121±23	114±21
White blood cell count (x 10 ⁹)	11.5(7.9-18.5)	8.5(2.4-16.9)	20.2(8.6-21.1)	9.4(6.0-15.6)	10.6(5.8-15.5)	12.1(6.6-16.7)	16.6(16.6-16.6)	10.6(10.4-10.8)
Plasma sodium (mmol x l ⁻¹)	134±5	135±4	133±5	133±5	135±6	135±6	134±5	135±5
Plasma potassium	4.1±0.7	4.1±0.6*	4.1±0.7	3.8±0.7*	4.4±0.6	4.6±0.7	4.4±0.7	4.5±0.7

(mmol x l ⁻¹)									
Plasma chloride (mmol x l ⁻¹)	101±5	102±6	102±7	103±6	101±5	102±5	103±5	106±6	
Plasma creatinine (μmol x l ⁻¹)	107(71-149)	129(72-160)	148(90-150)	77(57-94)	146(84-197)	150(85-162)	116(38-194)	103(77-274)	
Plasma Albumin (g x l ⁻¹)	33±6	32±7	31±5	26±11	29(22-32)	32(29-38)	26(26-26)	23(18-27)	

^R Range *p<0.05 ***p<0.001

Table A4. Mortality in severely hypotensive patients at 6 hours (i.e. the failed early resuscitation group vs. the rest)

BP at 6h	Alive at 28 days	Count	Percent
Severely hypotensive at 6h	Y	12	71
	N	5	29
Normotensive at 6h	Y	30	68
	N	14	32
Hypotensive at 6 h	Y	28	80
	N	7	20
Missing data	Y	5	

No difference between mortality ratios.

Table A5. Physiological changes over time in the hypotensive on arrival, severely hypotensive on arrival, hypotensive in the ED, severely hypotensive in the ED groups

Group based on timing of hypotension	Hypotensive on arrival		Severely hypotensive on arrival		Normotensive on arrival, hypotensive later		Normotensive on arrival, severely hypotensive later	
n	25		21		20		35	
Mortality at 30 days (%)	16		38		10		34	
	0h	6h	0h	6h	0h	6h	0h	6h
Crystalloids administered (ml)	-	1700(220-3670) ^R	-	1700(200-6000) ^R	-	1200(290-3630) ^R	-	1350(320-4400) ^R
Colloids administered (ml)	-	0(0-200) ^R	-	0(0-1370) ^R	-	0(0-0) ^R	-	0(0-1000) ^R
Packed red cells administered (ml)	-	0(0-0) ^R	-	0(0-180) ^R	-	0(0-0) ^R	-	0(0-150)
Fresh frozen plasma administered (ml)	-	0(0-0) ^R	-	0(0-150) ^R	-	0(0-0) ^R	-	0(0-300)
Platelets administered (ml)	-	0(0-0) ^R	-	0(0-0) ^R	-	0(0-0) ^R	-	0(0-200)
Fraction of inspired O ₂	0.21(0.21-0.36)	0.28(0.21-0.32)	0.21(0.21-0.28)	0.28(0.21-0.32)	0.21(0.21-0.21)	0.21(0.21-0.32)	0.28(0.21-0.44)	0.25(0.21-0.33)
Body temperature (°C)	37.1±1.6	37.0±1.2	37.1±1.4	36.3±1.4	37.6±1.3	36.6±0.9	37.4±1.3	36.6±0.8
Heart rate (x min ⁻¹)	104±29	96±20	104±27	92±20	110±15	92±25	108±32	89±22
Systolic blood pressure (mm Hg)	95±4	104±24	78±11	100±21	124±19	102±10	118±17	102±16
Diastolic blood pressure (mm Hg)	54±8	62±16	45±8	54±12	67±11	59±11	74±14	59±16
Mean arterial pressure (mmHg)	71±5	76±17	56±8	70±14	86±10	73±9	88±14	73±13
Respiratory rate (x min ⁻¹)	20(16-24)	20(18-22)	18(16-20)	18(18-20)	19(17-26)	19(17-24)	21(18-28)	18(16-23)
Arterial SaO ₂	97(94-98)	98(96-100)	97(94-99)	98(97-100)	97(94-99)	98(97-99)	98(94-100)	97(96-99)
Arterial pH	7.40±0.10	7.39±0.14	7.32±0.09	7.35±0.06	7.36±0.08	-	7.35±0.11	7.38±0.12
Arterial PaO ₂ (mm Hg)	-	104±71	-	112±36	133±111	-	93±52	102±29
Arterial PaCO ₂ (mm Hg)	41±8	39±11	42±9	40±6	46±17	-	46±16	41±15
Plasma base excess (mmol x l ⁻¹)	-1.4±4.7	-2.9±6.4	-4.3±5.7	-2.5±4.8	-0.5±4.8	-	-2.2±5.2	-2.0±3.9
Plasma lactate (mmol/litre)	2.1(1.4-2.4)	1.8(1.4-4.7)	2.3(1.5-3.0)	2.0(1.6-2.8)	1.3(1.2-1.9)	-	2.0(1.3-2.5)	1.7(1.5-2.2)
Blood haemoglobin (g x l ⁻¹)	123±20	110±17	115±28	123±18	129±25	-	123±22	116±17
White blood cell count (x 10 ⁹)	10.7(7.1-16.2)	-	12.4(10.4-21.2)	-	9.6(7.4-17)	-	10.9(7.0-16.6)	-
Plasma sodium (mmol x l ⁻¹)	135±5	132±5	132±5	133±3	135±6	-	135±4	134±5
Plasma potassium (mmol x l ⁻¹)	4.0±0.6	4.0±1.1	4.4±0.8	4.3±0.6	4.0±0.6	-	4.4±0.7	3.9±0.5

Plasma chloride (mmol x l ⁻¹)	101±6	101±7	100±5	104±3	100±5	-	102±5	105±5
Plasma creatinine (μmol x l ⁻¹)	107(72- 133)	-	142(85- 216)	-	107±46	-	138(65- 160)	-
Plasma Albumin (g x l ⁻¹)	32±6	-	30±8	-	32±7	-	33±6	-

^R Range