Supplementary Online Content

Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.10485

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

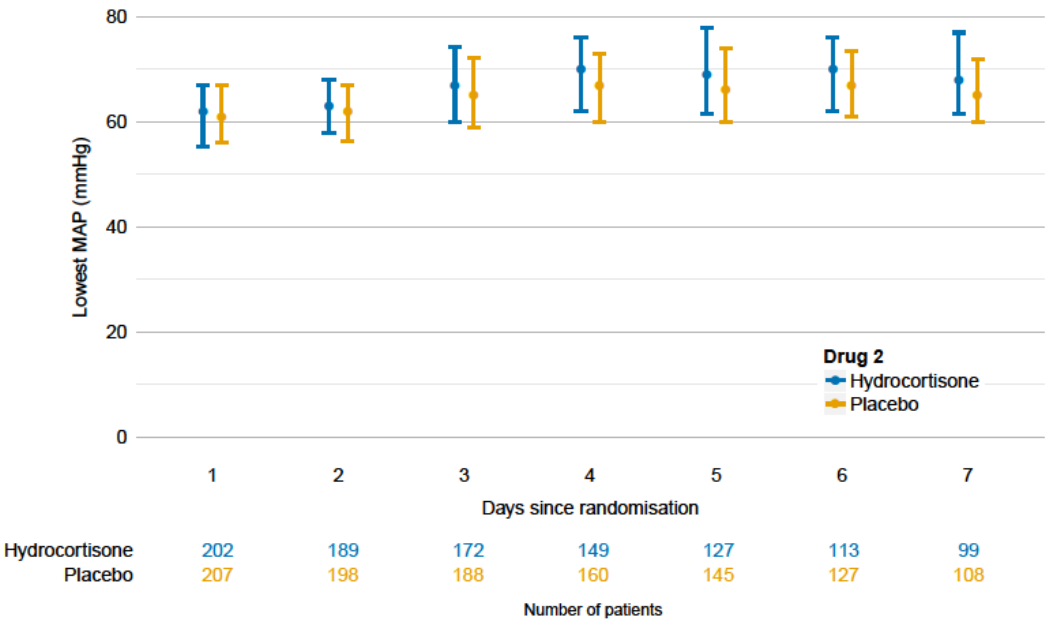
eMethods:

There were 5.6% of the daily serum creatinine or urine output values missing to calculate the daily Acute Kidney Injury (AKI) scores.[1] Last observation carried forward was used to impute missing serum creatinine values, as it was judged reasonable to assume that data were not collected because no change was expected by the clinician and 83% of missing values were for a single day only. This process resulted in a complete set of AKI scores for each patient while in ICU. If the patient's "normal" baseline creatinine value required to calculate AKI scores were unknown (57 patients), then these were estimated using the lowest creatinine value of the measurement at randomization, the measurement for APACHE II score calculation (within the 24 hours prior to randomization) and, provided the patient did not have chronic renal failure, the calculated value from the Modification of Diet in Renal Disease equation as proposed by the Acute Dialysis Quality Initiative.[2] Urine output was missing for <0.5% of scores. The overall AKI score was calculated using serum creatinine only where urine output values were missing. For the urine output-only AKI score, last observation carried forward was used to impute missing urine scores.

There were 6.3% of daily variables missing to calculate daily SOFA scores. Last observation carried forward was also used to impute missing SOFA scores. Where scores were missing for 3 or more days in a row, a sensitivity analysis was carried out assigning the highest possible score on missing days to the vasopressin patients and the lowest possible score to the norepinephrine patients and vice versa. These results were similar with no difference to the conclusions drawn (data not shown). This was repeated for the hydrocortisone and placebo groups, again with no difference to the conclusions (data not shown).

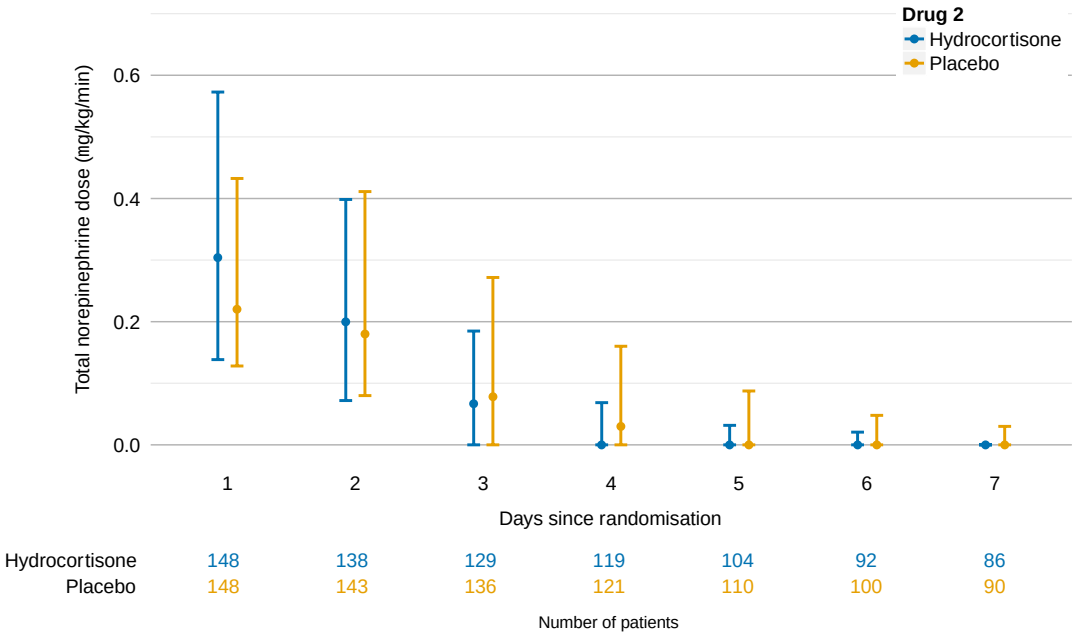
eFigure 1. Cardiovascular variables by study drug 2

a) Mean arterial pressure over the first seven days by study drug 2, intention to treat analysis



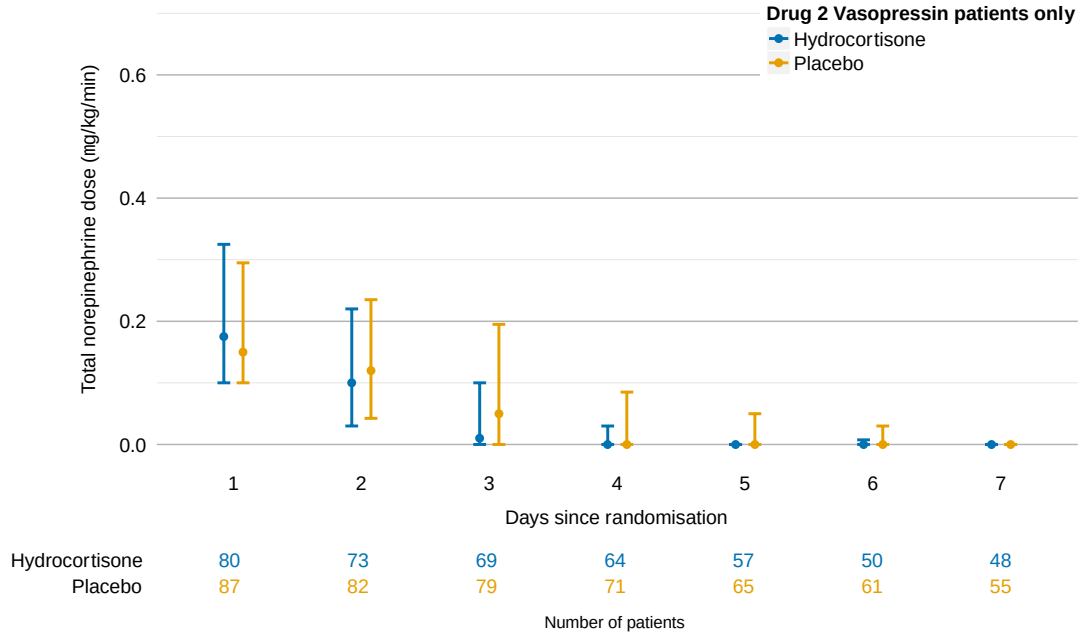
Number of patients	1	2	3	4	5	6	7
Hydrocortisone	202	189	172	149	127	113	99
Placebo	207	198	188	160	145	127	108

b) Maximum total norepinephrine dose over the first seven days for all patients given study drug 2, "per protocol" analysis

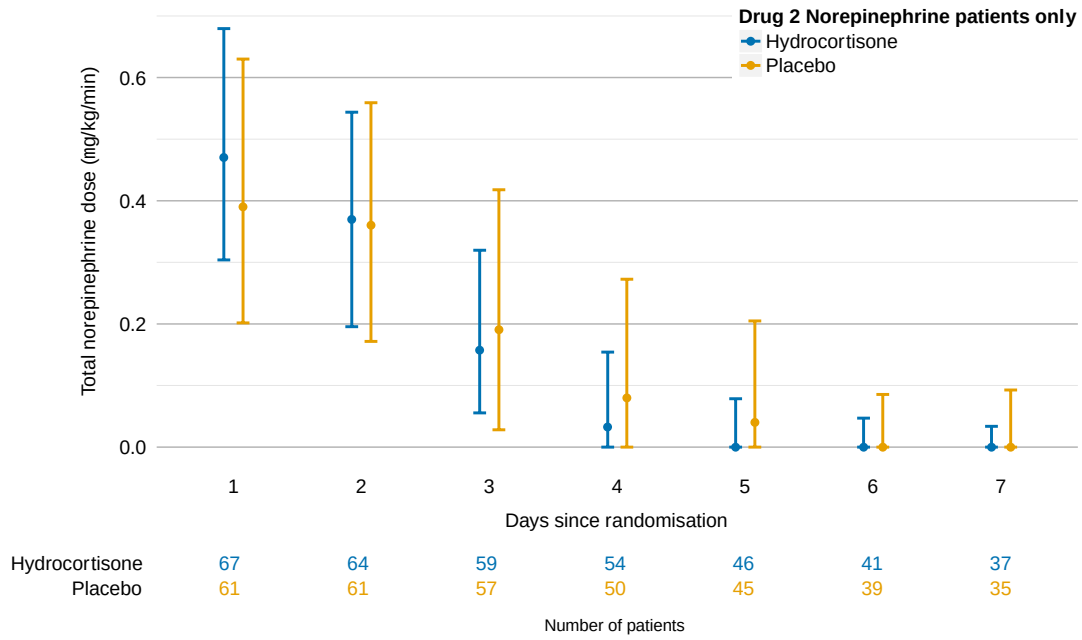


Number of patients	1	2	3	4	5	6	7
Hydrocortisone	148	138	129	119	104	92	86
Placebo	148	143	136	121	110	100	90

c) Maximum total norepinephrine dose over the first seven days for those vasopressin-group patients given study drug 2, “per protocol” analysis

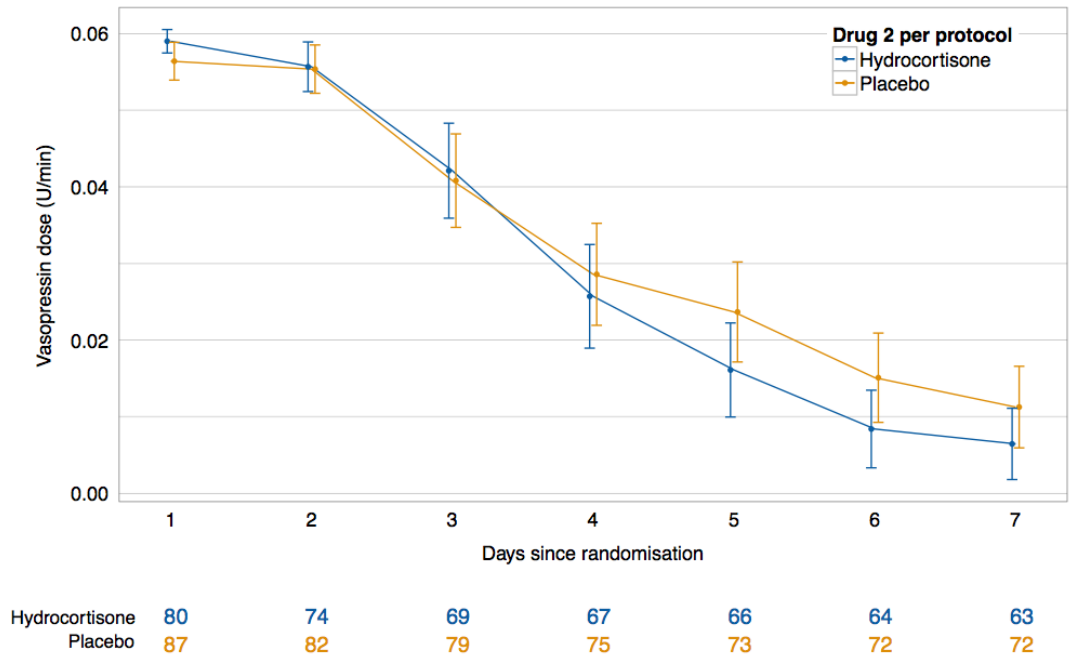


d) Maximum total norepinephrine dose over the first seven days for those norepinephrine-group patients given study drug 2, “per protocol” analysis



Blue circles represent the median for hydrocortisone patients, yellow circles for placebo patients. The vertical lines represent the interquartile range. Note that day 1 runs from the time of randomization to the end of the “ICU calendar day” so is therefore less than 24 hours and varies between patients.

eFigure 2. Maximum vasopressin dose over the first seven days for those patients given study drug 2, “per protocol” analysis

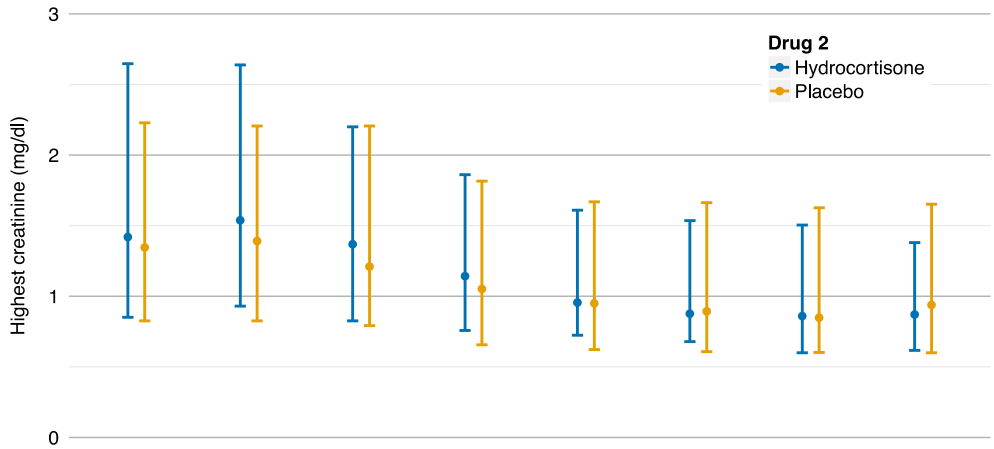


Hydrocortisone	80	74	69	67	66	64	63
Placebo	87	82	79	75	73	72	72

Blue line represents the mean for hydrocortisone patients, yellow line for placebo patients and vertical lines are 95% confidence intervals. Note that day 1 runs from the time of randomization to the end of the “ICU calendar day” so is therefore less than 24 hours and varies between patients.

eFigure 3. Kidney variables by study drug 2

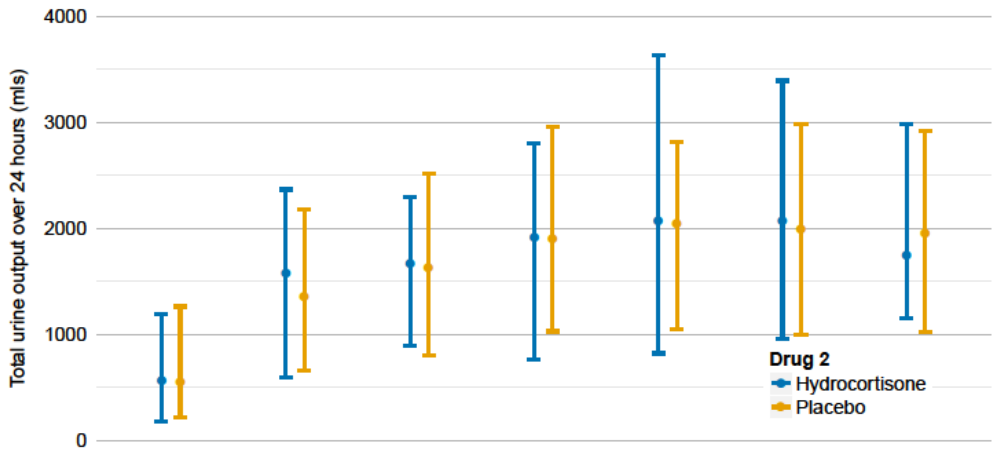
a) Serum creatinine over the first seven days



Hydrocortisone	202	202	186	171	148	126	113	99
Placebo	205	204	197	179	156	144	126	109

Number of patients

b) Urine output over the first seven days



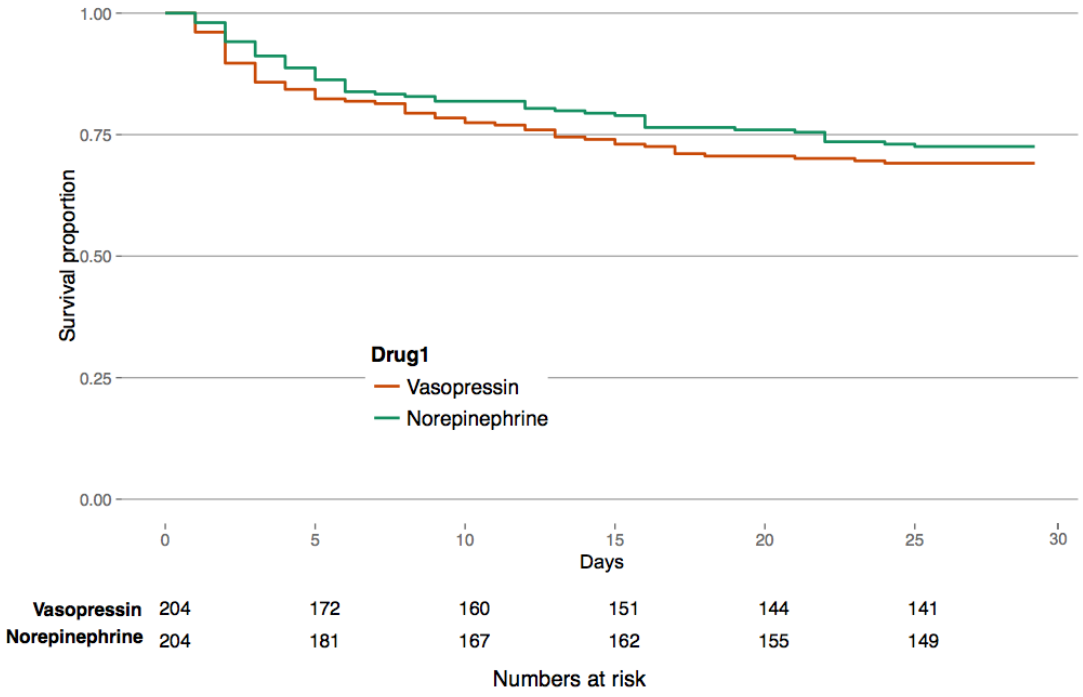
Hydrocortisone	202	189	173	153	131	115	101
Placebo	207	198	188	162	146	128	112

Number of patients

Blue circles represent the median for hydrocortisone patients, yellow circles for placebo patients, “intention to treat” analysis. The vertical lines represent the interquartile range. Day 0 = baseline. Note that day 1 runs from the time of randomization to the end of the “ICU calendar day” so it is therefore less than 24 hours and varies between patients.

eFigure 4. Kaplan-Meier Survival Curves

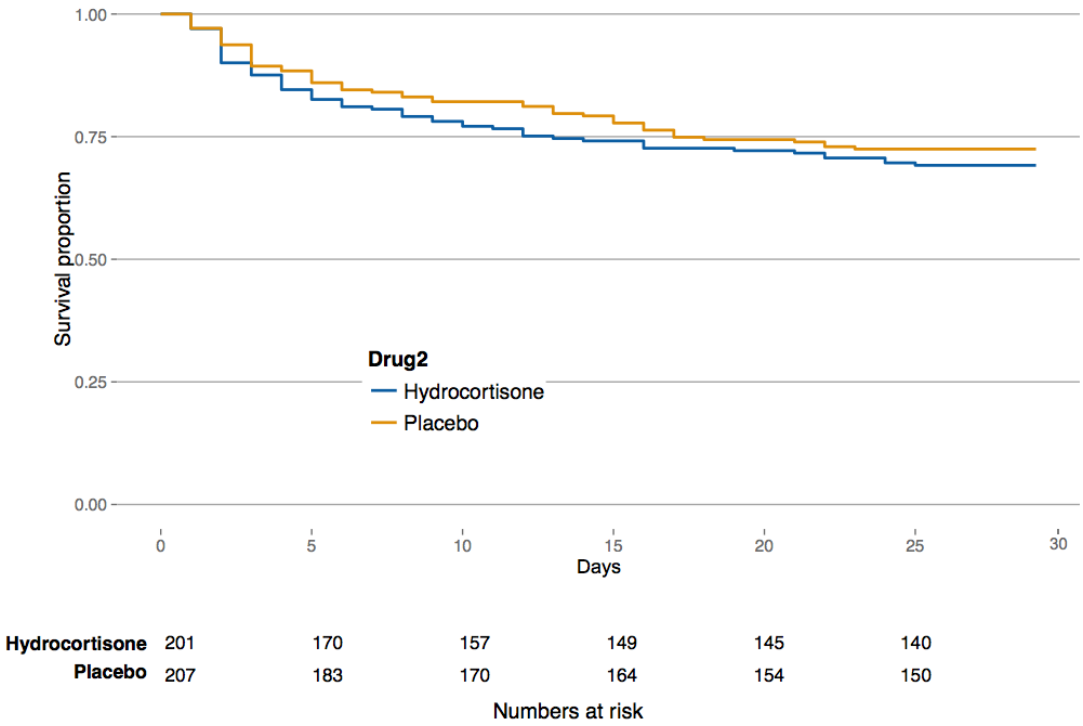
a) Vasopressin vs Norepinephrine



Vasopressin	204	172	160	151	144	141
Norepinephrine	204	181	167	162	155	149

Numbers at risk

b) Hydrocortisone vs Placebo



Hydrocortisone	201	170	157	149	145	140
Placebo	207	183	170	164	154	150

Numbers at risk

eTable 1. Numbers of missing baseline characteristics

	Vasopressin + hydrocortisone N=101	Vasopressin + placebo N=104	Norepinephrine + hydrocortisone N=101	Norepinephrine + placebo N=103	Total trial population N=409
Age	0	0	0	0	0
Male sex	0	0	0	0	0
Weight	0	0	1	0	1
Body Mass Index	7	3	5	4	19
Caucasian ethnicity	0	0	0	0	0
Recent surgical history	0	0	0	0	0
APACHE II score	0	0	0	1	1
Pre-existing conditions	0	0	0	0	0
Organ failure					
Respiratory	2	2	1	2	7
Renal	0	1	0	0	1
Liver	5	9	5	11	30
Haematological	0	4	3	4	11
Neurological	8	5	6	5	24
Physiological variables					
Mean Arterial Pressure	0	0	2	1	3
Heart Rate	0	0	0	1	1
Central venous pressure	39	48	40	48	175
Lactate	4	1	3	1	9
PaO_2/FiO_2	9	5	5	2	21
Creatinine	0	2	0	0	2
Bilirubin	5	9	5	11	30
Platelets	0	4	3	4	11
GCS	8	5	6	5	24
Mechanical ventilation	0	0	0	0	0
Renal Replacement therapy	0	0	0	0	0
Volume of IV fluid in previous 4 hours	2	0	2	0	4
Patients receiving other vasopressor at randomization	0	0	0	0	0
Time from onset of shock to receiving first study drug	0	0	0	0	0
Norepinephrine dose at randomization	0	0	0	0	0
Source of infection	3	2	3	1	9

APACHE – Acute Physiology and Chronic Health Evaluation, GCS- Glasgow Coma Score

eTable 2. Primary analysis of renal failure days using serum creatinine only criteria, and urine output only criteria

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute difference (95% CI)
	Hydrocortisone	Placebo	**Total**	Hydrocortisone	Placebo	**Total**	
Serum creatinine criteria only (N)	100	104	204	101	103	204	
28-day survivors who never developed renal failure, N/Total (%)[a]	53/81 (65.4)	58/84 (69.0)	111/165 (67.3)	55/77 (71.4)	56/80 (70.0)	111/157 (70.7)	-3.4 (-13.5, 6.7)
Renal failure free days in other patients[b], days, median (IQR)	7 (1-24)	12 (1-22)	9 (1-23)	12 (1-25)	14 (4-23)	12 (2-24)	-2 (-10, 6)
Urine output criteria only (N)	99[c]	104	203	101	103	204	
28-day survivors who never developed renal failure, N/Total (%)[a]	48/80 (60.0)	50/84 (59.5)	98/164 (59.8)	52/77 (67.5)	49/80 (61.3)	101/157 (64.3)	-4.6 (-15.2, 6.0)
Renal failure free days in other patients[b], days, median (IQR)	7 (1,24)	14 (1,27)	10 (1,25)	15 (1,25)	15 (1,27)	15 (1,27)	-5 (-11, 5)

The serum creatinine only and urine output only criteria are defined by the Acute Kidney Injury Network (AKIN) group stage 3 definition[1]

[a] 28 day survivors as a proportion of patients with no renal failure at baseline (one subject with no baseline renal failure data was excluded)

[b] Other patients = those who died and / or had renal failure at any time.

[c] Excludes one subject where renal free failure days could not be calculated due to missing urine data

eTable 3. Primary analysis of renal failure days and mortality analyses on an "as-treated" analysis and "per protocol analysis"

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute difference (95% CI)
	Hydrocortisone	Placebo	**Total**	Hydrocortisone	Placebo	**Total**	
As treated analysis	N=84	N=122	N=206	N=73	N=129	N=202	
28-day survivors who never developed renal failure, N/Total (%)[a]	36/66 (54.5)	58/100 (58.0)	94/166 (56.6)	26/55 (47.3)	67/101 (66.3)	93/156 (59.6)	-3.0 (-13.8,7.8)
Renal failure free days in other patients[b], days, median (IQR)	4 (0-21)	13 (1-25)	8 (1-24)	13 (0-25)	14 (1-25)	14 (1-25)	-6 (-11, 4)
28-day mortality, N/Total (%)	31/84 (36.9)	33/122 (27.0)	64/206 (31.1)	26/73 (35.6)	29/129 (22.5)	55/202 (27.2)	3.8 (-5.0, 12.7)
ICU mortality, N/Total (%)	30/84 (35.7)	29/122 (23.8)	59/206 (28.6)	22/73 (30.1)	28/129 (21.7)	50/202 (24.8)	3.9 (-4.7, 12.5)
Hospital mortality, N/Total (%)	33/84 (39.3)	36/122 (29.5)	69/206 (33.5)	26/73 (35.6)	33/129 (25.6)	59/202 (29.2)	4.3 (-4.7, 13.3)
Per protocol analysis	N=79	N=87	N=166	N=67	N=61	N=128	
28-day survivors who never developed renal failure, N/Total (%)[a]	35/62 (56.5)	36/69 (52.2)	71/131(54.2)	24/49 (49)	24/47 (51.1)	48/96 (50.0)	4.2 (-8.9, 17.3)
Renal failure free days in other patients[b], days, median (IQR)	5 (0-21)	12 (1-25)	9 (0-24)	13 (0-25)	14 (1-22)	14 (0-24)	-5 (-11,6)
28-day mortality, N/Total (%)	28/79 (35.4)	27/87 (31.0)	55/166 (33.1)	24/67 (35.8)	20/61 (32.8)	44/128 (34.4)	-1.2 (-12.1, 9.7)
ICU mortality, N/Total (%)	27/79 (34.2)	24/87 (27.6)	51/166 (30.7)	20/67 (29.9)	20/61 (32.8)	40/128 (31.3)	-0.5 (-11.2, 10.1)
Hospital mortality, N/Total (%)	30/79 (38.0)	30/87 (34.5)	60/166 (36.1)	24/67 (35.8)	21/61 (34.4)	45/128 (35.2)	1.0 (-10.0, 12.0)

[a] 28 day survivors as a proportion of patients with no renal failure at baseline (one subject with no baseline renal failure data was excluded
[b] Other patients = those who died and / or had renal failure at any time.

eTable 2. Mean intravenous fluid volume administered over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo.

a)

	Vasopressin		Norepinephrine		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	205	2889 ± 3813	204	2805 ± 2455	84	(-539,708)
Day 2	189	3180 ± 2204	198	2934 ± 2182	246	(-192,685)
Day 3	180	2257 ± 1811	182	2087 ± 1733	170	(-196,537)
Day 4	158	1817 ±1620	157	1743 ±1412	74	(-263,411)
Day 5	144	1746 ±1736	133	1657 ±1331	89	(-276,453)
Day 6	130	1774 ± 1449	113	1501 ± 1316	273	(-77,622)
Day 7	114	1569 ± 1150	100	1482 ± 1363	87	(-256,429)

[a] Mean difference Vasopressin – Norepinephrine; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

b)

	Hydrocortisone		Placebo		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	202	3021 ± 4015	207	2678 ± 2135	343	(-284,971)
Day 2	189	3061 ± 2075	198	3047 ± 2306	14	(-425,451)
Day 3	174	2292 ± 1970	188	2060 ± 1564	232	(-138,601)
Day 4	153	1812 ± 1692	162	1750 ± 1337	62	(-277,402)
Day 5	131	1798 ± 1791	146	1618 ± 1302	180	(-194,554)
Day 6	115	1757 ± 1588	128	1548 ± 1188	209	(-148,567)
Day 7	101	1659 ± 1349	113	1411 ± 1151	248	(-92,588)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

eTable 3. Mean total fluid balance over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo.

a)

	Vasopressin		Norepinephrine		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	204	2071 ± 2064	204	1885 ± 2318	186	(-242,612)
Day 2	189	1949 ± 2256	198	1626 ± 2347	323	(-137,783)
Day 3	177	698 ± 1974	182	554 ± 1839	144	(-252,540)
Day 4	158	137 ± 1559	157	52 ± 1827	85	(-292,462)
Day 5	144	-237 ± 1708	133	19 ± 1831	-256	(-676,164)
Day 6	129	-119 ± 1718	113	-84 ± 1642	-35	(-461,391)
Day 7	115	-16 ± 1339	99	142 ± 1302	-158	(-515,198)

[a] Mean difference Vasopressin – Norepinephrine; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

b)

	Hydrocortisone		Placebo		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	201	2001 ± 2243	207	1955 ± 2151	46	(-382,474)
Day 2	189	1774 ± 2012	198	1794 ± 2560	-20	(-479,439)
Day 3	173	711 ± 2099	186	545 ± 1708	166	(-234,564)
Day 4	153	221 ± 1608	162	-25 ± 1772	246	(-129,620)
Day 5	131	-105 ± 1912	146	-122 ± 1637	17	(-407,441)
Day 6	114	20 ± 1838	128	-211 ± 1524	231	(-200,661)
Day 7	102	111 ± 1294	112	7 ± 1349	104	(-252,460)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

eTable 4. Mean serum lactate over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo

a)

	Vasopressin		Norepinephrine		Difference[a] (mmol/L)	95% CI
	N[b]	Mean ± SD (mmol/L)	N[b]	Mean ± SD (mmol/L)		
Day 1	198	3.8 ± 3.5	194	3.6 ± 3.3	0.3	(-0.4,1.0)
Day 2	179	3.2 ± 2.8	190	3.2 ± 3.2	0.1	(-0.6,0.8)
Day 3	171	2.5 ± 2.8	171	2.6 ± 3.3	-0.1	(-0.8,0.6)
Day 4	144	2.5 ± 2.8	139	2.4 ± 3.1	-0.3	(-0.9,0.3)
Day 5	127	1.9 ± 1.5	120	1.9 ± 2.2	0.1	(-0.5,0.6)
Day 6	109	1.9 ± 1.3	98	1.9 ± 2.2	0.0	(-0.6,0.5)
Day 7	101	1.7 ± 0.8	90	1.7 ± 1.2	0.1	(-0.4,0.6)

[a] Mean difference Vasopressin – Norepinephrine; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

b)

	Hydrocortisone		Placebo		Difference[a] (mmol/L)	95% CI
	N[b]	Mean ± SD (mmol/L)	N[b]	Mean ± SD (mmol/L)		
Day 1	196	3.8 ± 3.5	196	3.7 ± 3.4	0.1	(-0.5,0.8)
Day 2	179	3.2 ± 2.8	190	3.3 ± 3.8	-0.1	(-0.9,0.5)
Day 3	164	2.5 ± 2.8	178	2.6 ± 3.4	-0.1	(-0.8,0.5)
Day 4	136	2.5 ± 2.8	147	2.0 ± 2.3	0.5	(-0.2,1.0)
Day 5	116	1.9 ± 1.5	131	2.0 ± 2.5	-0.1	(-0.6,0.4)
Day 6	99	1.9 ± 1.3	108	1.9 ± 2.4	0.0	(-0.6,0.5)
Day 7	93	1.7 ± 0.8	98	1.9 ± 2.4	-0.2	(-0.7,0.3)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

eTable 7. Mean highest heart rate over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo

a)

	Vasopressin		Norepinephrine		Difference[a] (beats / minute)	95% CI
	N[b]	Mean ± SD (beats / minute)	N[b]	Mean ± SD (beats / minute)		
Day 1	205	106 ± 23	204	108 ± 22	-2	(-6,3)
Day 2	189	103 ± 24	198	109 ± 20	-6	(-10,-1)
Day 3	178	106 ± 27	182	107 ± 22	-1	(-6,4)
Day 4	158	105 ± 24	156	106 ± 21	-1	(-6,4)
Day 5	144	107 ± 25	133	108 ± 23	-1	(-7,4)
Day 6	131	105 ± 22	114	104 ± 19	1	(-4,6)
Day 7	115	104 ± 22	100	102 ± 19	2	(-3,8)

[a] Mean difference Vasopressin – Norepinephrine; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

b)

	Hydrocortisone		Placebo		Difference[a] (beats / minute)	95% CI
	N[b]	Mean ± SD (beats / minute)	N[b]	Mean ± SD (beats / minute)		
Day 1	202	108 ± 23	207	106 ± 22	2	(-2,7)
Day 2	189	105 ± 22	198	107 ± 22	-2	(-6,2)
Day 3	172	105 ± 25	188	107 ± 23	-2	(-7,3)
Day 4	152	103 ± 22	162	107 ± 23	-4	(-9,1)
Day 5	131	105 ± 22	146	110 ± 26	-5	(-10,2)
Day 6	116	106 ± 22	129	102 ± 19	4	(-1,9)
Day 7	102	104 ± 23	113	103 ± 19	1	(-4,7)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

eTable 6. Mean serum creatinine over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo

a)

	Vasopressin		Norepinephrine		Difference[a] (mg/dl)	95% CI
	N[b]	Mean ± SD (mg/dl)	N[b]	Mean ± SD (mg/dl)		
Day 1	202	1.74 ± 1.16	204	1.96 ± 1.71	-0.22	(-0.51,0.06)
Day 2	186	1.55 ± 1.06	197	1.74 ± 1.31	-0.19	(-0.43,0.04)
Day 3	175	1.33 ± 0.91	175	1.56 ± 1.16	-0.23	(-0.45,-0.01)
Day 4	153	1.20 ± 0.91	151	1.45 ± 1.12	-0.25	(-0.48,-0.02)
Day 5	141	1.15 ± 0.91	129	1.45 ± 1.15	-0.30	(-0.55,-0.05)
Day 6	127	1.12 ± 0.82	112	1.42 ± 1.21	-0.30	(-0.57,-0.03)
Day 7	111	1.13 ± 0.80	97	1.34 ± 1.12	-0.21	(-0.48,0.06)

[a] Mean difference Vasopressin – Norepinephrine; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

b)

	Hydrocortisone		Placebo		Difference[a] (mg/dl)	95% CI
	N[b]	Mean ± SD (mg/dl)	N[b]	Mean ± SD (mg/dl)		
Day 1	202	1.98 ± 1.71	204	1.72 ± 1.17	0.26	(-0.03,0.54)
Day 2	186	1.74 ± 1.29	197	1.56 ± 1.10	0.18	(-0.07,0.41)
Day 3	171	1.48 ± 1.02	179	1.42 ± 1.07	0.06	(-0.16,0.28)
Day 4	148	1.35 ± 1.04	156	1.30 ± 1.01	0.05	(-0.19,0.27)
Day 5	126	1.30 ± 1.11	144	1.29 ± 0.98	0.01	(-0.24,0.27)
Day 6	113	1.24 ± 1.09	126	1.27 ± 0.98	-0.03	(-0.30,0.23)
Day 7	99	1.18 ± 0.97	109	1.28 ± 0.96	-0.10	(-0.36,0.17)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean

eTable 7. Mean urine output over the first 7 days, a) vasopressin vs norepinephrine and b) hydrocortisone vs placebo.

a)

	Vasopressin		Norepinephrine		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	205	737 ± 3813	204	1010 ± 2455	-273	(-454, -94)
Day 2	189	1521 ± 2204	198	1628 ± 2182	-107	(-357, 142)
Day 3	179	1833 ± 1811	182	1680 ± 1733	153	(-120, 427)
Day 4	158	2199 ± 1620	157	1946 ± 1412	253	(-93, 598)
Day 5	144	2451 ± 1736	133	2027 ± 1331	424	(32, 815)
Day 6	129	2382 ± 1449	114	2062 ± 1316	320	(-106, 746)
Day 7	114	2314 ± 1150	99	1906 ± 1363	408	(11, 804)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

b)

	Hydrocortisone		Placebo		Difference[a] (mls)	95% CI
	N[b]	Mean ± SD (mls)	N[b]	Mean ± SD (mls)		
Day 1[c]	202	851 ± 4015	207	895 ± 2135	-44	(-226, 138)
Day 2	189	1555 ± 2075	198	1595 ± 2306	-40	(-290, 210)
Day 3	173	1753 ± 1970	188	1758 ± 1564	-5	(-279, 269)
Day 4	153	2022 ± 1692	162	2120 ± 1337	-98	(-445, 249)
Day 5	131	2318 ± 1791	146	2184 ± 1302	134	(-262, 530)
Day 6	115	2314 ± 1588	128	2158 ± 1188	156	(-277, 589)
Day 7	101	2131 ± 1349	112	2118 ± 1151	13	(-389, 414)

[a] Mean difference Hydrocortisone – Placebo; figures may not add due to rounding
[b] Number of subjects included in calculation of the mean
[c] Day 1 runs from the time of randomization to the end of the "ICU calendar day" so it is therefore less than 24 hours and varies between patients.

eTable 10. Analysis of other organ failure–free days

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute difference (95% CI)
	Hydrocortisone	Placebo	**Total**	Hydrocortisone	Placebo	**Total**	
28-day survivors who never developed respiratory failure, N/Total (%)[a]	29/66 (43.9)	27/63 (42.9)	56/129 (43.4)	26/60 (43.3)	37/63 (58.7)	63/123 (51.2)	-8.1 (-20.4,4.1)
Respiratory failure free days in other patients[b], days, median (IQR)	10 (1,23)	18 (2,24)	16 (1,24)	18 (2,25)	18 (3,26)	18 (3,25)	-2 (-9,5)
28-day survivors who never developed liver failure, N/Total (%)[a]	58/92 (63.0)	62/91 (68.1)	120/183 (65.6)	58/90 (64.4)	61/86 (70.9)	119/176 (67.6)	-2.0 (-11.8,7.7)
Liver failure free days in other patients[b], days, median (IQR)	4 (1,10)	4 (1,16)	4 (1,14)	8 (1,21)	5 (2,20)	6 (2,21)	-2 (-10,3)
28-day survivors who never developed hematological failure, N/Total (%)[a]	55/94 (58.5)	56/94 (59.6)	111/188 (59.0)	58/92 (63.0)	69/95 (72.6)	127/187 (67.9)	-8.1 (-18.9,0.5)
Hematological failure free days in other patients[b], days, median (IQR)	6 (1,20)	12 (1,23)	8 (1,23)	7 (2,22)	6 (1,16)	6 (1,21)	2 (-8,7)
Cardiovascular failure free days in all patients, median (IQR)	22 (3,25)	22 (6,25)	22 (5,25)	24 (9,26)	25 (10,26)	24 (9,26)	-2 (-4,0)

[a] 28 day survivors as a proportion of patients with no organ failure at baseline, excluding the following subjects with missing baseline organ failure data (7 for respiratory failure, 30 for liver failure, 11 for hematological failure)

[b] Other patients = those who died and / or had the corresponding acute organ failure at any time.

eTable 11. Outcome data comparing hydrocortisone groups with placebo groups

	Hydrocortisone Total	**Placebo Total**	Hydrocortisone vs placebo, Absolute difference[a] (95% CI)
28-day survivors who never developed renal failure, N/Total (%)[b]	92/158 (58.2)	95/164 (57.9)	0.3 (-10.5, 11.1)
Renal failure free days in other patients[c], days, median (IQR)	8 (0, 24)	14 (1, 25)	-6 (-12, 4)
28-day mortality, N/Total (%)	62/201 (30.8)	57/207 (27.5)	3.3 (-5.5, 12.1)
ICU mortality, N/Total (%)	56/201 (27.9)	53/207 (25.6)	2.3 (-6.3, 10.9)
Hospital mortality, N/Total (%)	66/201 (32.8)	62/207 (30.0)	2.9 (-6.1, 11.9)
Renal Failure, N/Total (%)	87/202 (43.1)	97/202 (46.9)	-3.8 (-13.4,5.8)
Duration of Renal Failure, days, median (IQR)	4 (1,7)	3 (1,8)	1 (-1, 2)
Survivors	4 (2,7)	4 (2,8)	0 (-2, 3)
Non-survivors	3 (1,7)	2 (1,6)	1 (-1, 2)
Use of renal replacement therapy, N/Total (%)	61/202 (30.2)	63/207 (30.4)	-0.2 (-9.1, 8.7)
Duration of renal replacement therapy, days median (IQR)	3 (2,7)	3 (2,8)	0 (-2,2)
Survivors	4 (2,8)	4 (2,14)	0 (-4,4)
Non-survivors	3 (2,6)	3 (2,5)	0 (-2,2)
Numbers weaned from vasopressors for >24hrs, N/Total (%)	179/202 (88.6)	179/207 (86.5)	-2.1 (-4.3, 8.5)
Time to shock reversal, hours median (IQR)	48 (27,82)	48 (24,97)	0 (-15,10)
Use of inotropes[d], N/Total (%)	55/202 (27.2)	41/207 (19.8)	7.4 (-0.8, 15.6)
Duration of mechanical ventilation, days median (IQR)	5 (2,12)	6 (3,12)	-1 (-3,1)
Mean total SOFA score, Mean ± SD	6.1 (3.2)	6.1 (3.3)	0.0 (-0.6, 0.7)
ICU length of stay, days median (IQR)	6 (3,11)	6 (3,12)	0 (-2,1)
Hospital length of stay, days median (IQR)	15 (7,34)	16 (8,39)	-1 (-6,2)
Patients who had one or more serious adverse events, N/Total (%)	20/202 (9.9)	19/207 (9.2)	0.7 (-5.0, 6.4)
Subcategories of serious adverse events[e]			
Digital ischemia, N/Total (%)	6/202 (3.0)	8/207 (3.9)	-0.9 (-4.9,3.1)
Mesenteric ischemia, N/Total (%)	6/202 (3.0)	4/207 (1.9)	1.0 (-2.5,4.5)
Life threatening arrhythmia, N/Total (%)	3/202 (1.5)	4/207 (1.9)	-0.4 (-3.4,2.5)
Acute Coronary Syndrome, N/Total (%)	6/202 (3.0)	3/207 (1.4)	1.5 (-1.8,4.9)
Other, N/Total (%)	5/202 (2.5)	3/207 (1.4)	1.0 (-2.2,4.2)

SOFA – Sequential Organ Failure Assessment (range 0-20, a higher score corresponds to more severe organ failure)

[a] Absolute difference in percentage for binary variables and difference in medians for continuous variables. 95% confidence intervals for the difference in medians calculated using bootstrapping; figures may not add due to rounding.
[b] 28 day survivors as a proportion of patients with no organ failure at baseline
[c] Other patients = those who died and / or had renal failure at any time.
[d] inotropes defined as dobutamine, epinephrine, milrinone, dopamine, dopexamine.
[e] The N of serious adverse events represents the number of patients who had that subcategory of event. Patients may have had more than one event.

eReferences.

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