Site of infection

- Pulmonary sepsis was the predominant source of infection in the medical patients.
- Gastrointestinal and abdominal sepsis was the predominant source of infection in the surgical patients.
- Rates of bacteraemia 35.4% (HC) vs 34.1% (Placebo)
- Breakdown of infection categories similar between the groups

Time intervals

	Hydrocortisone (N = 1853)	Placebo (N = 1860)
Time from ICU admission to randomisation (hours)	26.1 ± 70.7	28.9 ± 72.8
Time from inotropes use (shock) to randomisation (hours)	20.9 ± 91.9	21.2 ± 83.4
Time from randomisation to administration of study drug (minutes)	84.5 ± 162.7	79.6 ± 102.7

Study treatment

- Trial drug infused at a rate of 200mL/day
- Hydrocortisone concentration was 1mg/mL
- Patients received trial drug for 7 days or until ICU discharge, whichever was earlier.
- If patients completed entire 7 day course, then the maximal trial drug volume was 1400 ml.

Study treatment

Variable	Hydrocortisone (N=1835)	Placebo (N = 1829)	P-value
Cumulative dose of study drug received (ml)	968.7 ± 444.2	996.6 ± 450.3	0.06
Cumulative dose duration (days)	4.6 ± 2.2	4.8 ± 2.3	0.09
Overall compliance (%)	95.2 ± 11.3	94.9 ± 12.1	0.34

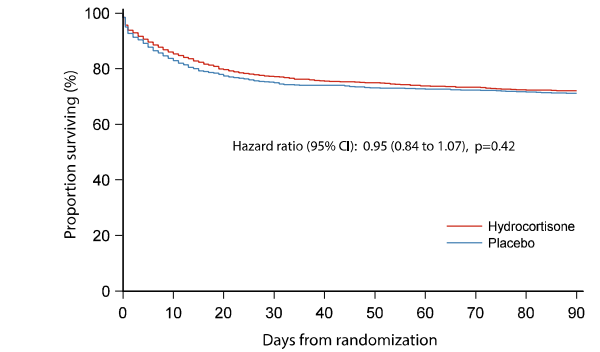
Concomitant therapies

Variable	Hydrocortisone (N=1835)	Placebo (N = 1829)	P-value
Open-label steroids	7.4%	8.8%	0.13
Etomidate post randomisation	1.3%	1.2%	0.88

Primary outcome – Day 90 mortality

	Hydrocortisone (N = 1832)	Placebo (N = 1826)	Odds Ratio	Lower 95%CI	Upper 95%CI	P-value
Unadjusted	511 (27.9%)	526 (28.8%)	0.96	0.83	1.10	0.54
Adjusted - stratification variables			0.95	0.82	1.10	0.50
Adjusted - additional covariates			0.96	0.82	1.12	0.58

Primary outcome – Time to death

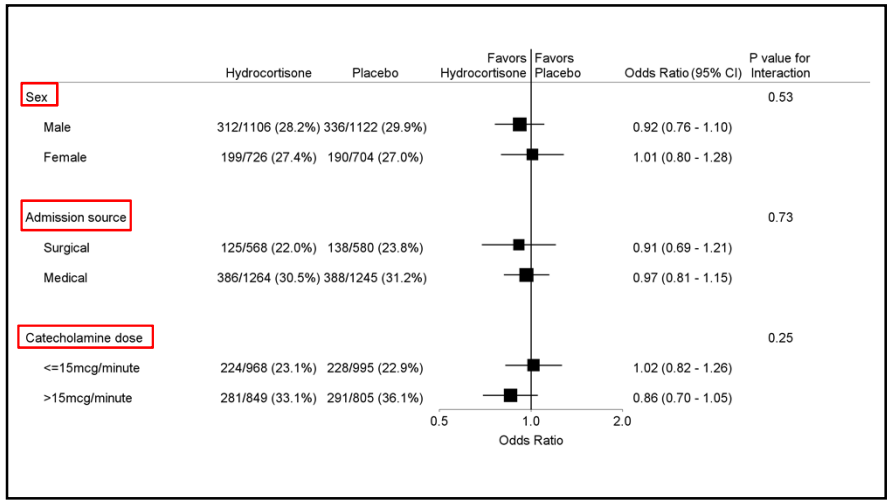


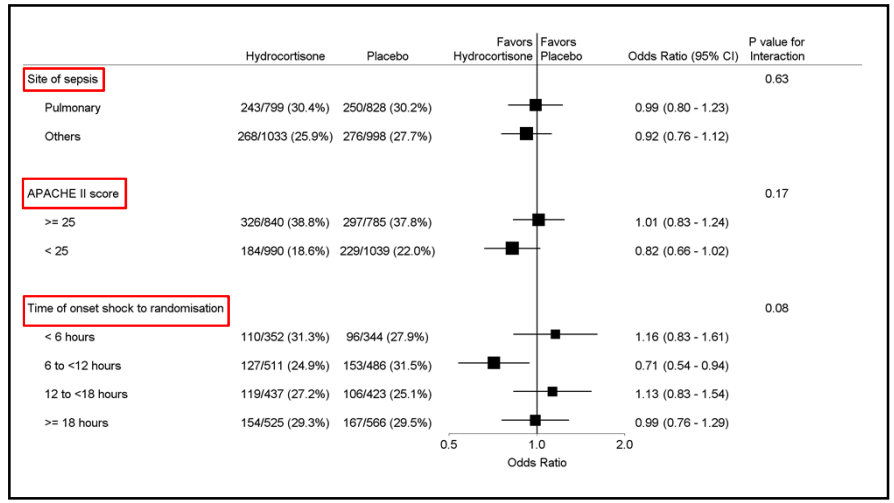
No. at risk

Hydrocortisone :	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo :	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

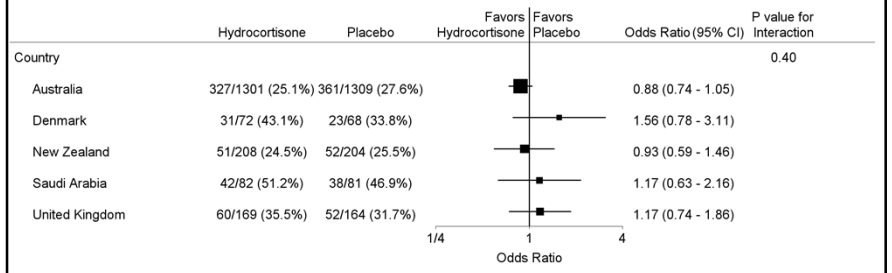
Pre-defined subgroups

- Sex
- Surgical vs Medical admission
- APACHE score < or ≥ 25
- Pulmonary vs non-pulmonary
- Noradrenaline dose < or ≥ 15 mcg/kg/min
- Time from onset of shock to randomisation in 6 hour time bands





Analysis of primary outcome by region



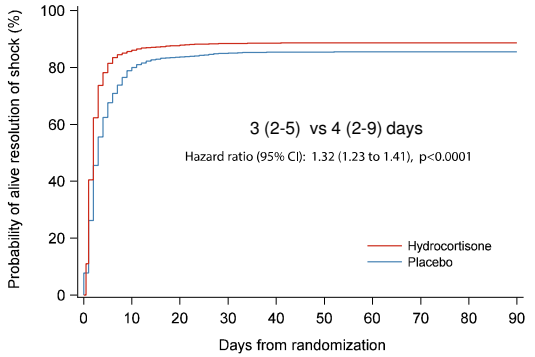
Post hoc-sensitivity analysis of primary outcome excluding patients who received open label steroids

OR 0.96, 95%CI 0.82 to1.12, P=0.59

Secondary outcomes

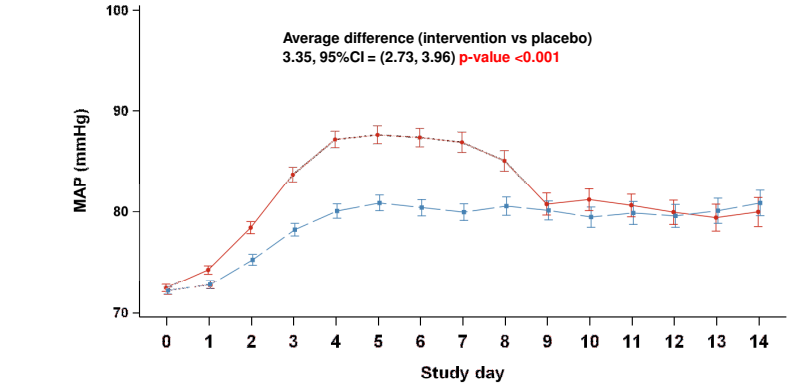
- Time to resolution of shock
- Recurrence of shock
- Duration of ICU and hospital admission
- Frequency and duration of mechanical ventilation
- Frequency and duration of RRT
- Episodes of new bacteraemia and fungaemia
- Episodes of clinically important bleeding in the ICU
- All-cause mortality 28 days & 6 months after randomisation

Sec outcome 1: Shock reversal



No. at Risk

Hydrocortisone :	1843	104	34	9	6	3	3	2	1	0
Placebo :	1854	213	53	19	8	6	4	0	0	0



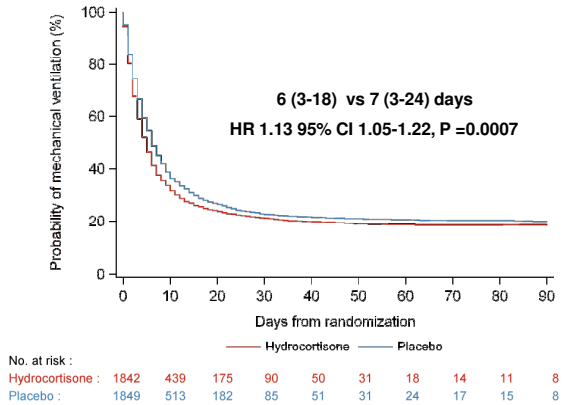
Number of patients :

Hydrocortisone	1849	1831	1814	1696	1515	1330	1174	1017	885	757	692	600	541	480	436
Placebo	1856	1835	1820	1693	1549	1415	1247	1097	979	850	742	667	602	552	491

Sec Outcome 2: Shock recurrence

Variable	Hydrocortisone (N = 1853)	Placebo (N = 1860)	Odds Ratio	Lower 95%CI	Upper 95%CI	P-value
Recurrence of shock	365 (19.7%)	343 (18.4%)	1.07	0.94	1.22	0.32

Sec Outcome 3: Time from randomization to cessation of IPPV

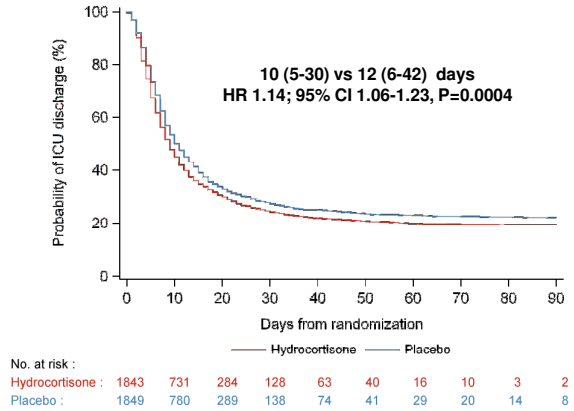


Sec outcome 4: Length of ventilation and recurrence of IPPV

Variable	Hydrocortisone (N = 1842)	Placebo (N = 1850)	Mean diff/ Rate Ratio 95% CI	P-value
Days alive and free of IPPV	61.2±35.6	59.1±36.1	2.18 (-0.11 to 4.46)	0.06
Re-ventilation rates	180 (9.8%)	154 (8.3%)	1.18 (0.96 to 1.45)	0.11

BV1

Sec outcome 5: Time from randomization to ICU discharge



Sec outcome 5: Length of ICU and hospital admission

Variable	Hydrocortisone (N = 1853)	Placebo (N = 1860)	Mean diff/ Rate Ratio 95% CI	P-value
Days alive and free of ICU	58.2 ±34.8	56.0 ±35.4	2.26 (0.04-4.49)	0.047 **0.005**
Days alive and free of Hospital	40.0 ±32	38.6 ±32.4	1.45 (-0.59-3.49)	0.163

Slide 59

BV1 Bala Venkatesh, 28/12/2017

Sec outcome 6: Renal replacement therapy

Variable	Hydrocortisone (N = 1853)	Placebo (N = 1860)	Mean diff/ Rate Ratio 95% CI	P-value
Days alive and free of RRT	42.6 ±39.1	40.4 ±38.5	2.37 (-2.00t o 6.75)	0.29
Any RRT received	567 (30.6%)	609 (32.7%)	0.94 (0.86 to 1.03)	0.18

Sec Outcome 7: Superinfection- new onset bacteraemia/fungaemia

Variable	Hydrocortisone (N = 1853)	Placebo (N = 1860)	Rate Ratio 95% CI	P-value
New bacteraemia fungaemia	262 (14.1%)	262 (14.1%)	1.00 (0.86-1.16)	0.96

Sec Outcome 8: Requirement for blood transfusion

Variable	Hydrocortisone	Placebo	Odds Ratio	95%CI	P-value
Blood transfusion	683/1848 (37.0)	773/1855 (41.7)	0.82	0.72 to 0.94	0.004

Sec Outcome 9: 28 day mortality

Variable	Hydrocortisone (N = 1841)	Placebo (N = 1840)	Odds Ratio	Lower 95%CI	Upper 95%CI	P-value
Mortality at Day 28						
Unadjusted	410 (22.3%)	448 (24.3%)	0.89	0.76	1.03	0.13
Adjusted - stratification variables			0.89	0.76	1.03	0.12

Adverse events

- 33 total (24 hydrocortisone vs 3 placebo)
  1.1% vs 0.3%, P =0.009
- Predominantly metabolic (high BSL and hypernatremia)
- Others include GI bleed, haematological and encephalopathy

- SAE – 4 (HC) vs 2 (Placebo)

Summary of principal findings

- Hydrocortisone did not lead to a significant reduction in mortality at 90 days in patients with septic shock
- This effect on mortality did not differ in any of the six pre-defined subgroups.
- Hydrocortisone - more rapid resolution of shock,
- Hydrocortisone - shorter duration of initial episode of IPPV
- Hydrocortisone – an earlier time to ICU discharge
- Hydrocortisone – reduced frequency of blood transfusion

Summary of principal findings

No significant differences between the two groups with respect to;

a) recurrence of shock
b) need for renal replacement therapy
c) recurrence of mechanical ventilation
d) volume of blood transfused and
e) new onset bacteraemia or fungaemia.

Adverse effects: A small but a slightly higher incidence of adverse effects in the hydrocortisone group, but these did not impact on patient-centred outcomes

Strengths of the study

Pragmatic trial, statistical power

Central randomization, allocation concealment

Blinding of trial-group assignments, independently verified

Publication of the SAP before unblinding

We specifically targeted a population of patients who had high requirements for vital organ support and a substantial risk of death.

High randomization to eligibility ratio, low rate of loss to follow up

External validity

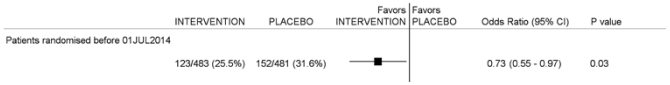
Key differences from previous trials

- Statistical power
- Time to enrolment
- Mechanical ventilation as an inclusion criterion
- Etomidate naïve patients
- Hydrocortisone by infusion
- No tapering strategy
- No corticotropin testing
- Did not use fludrocortisone

Comparative timelines

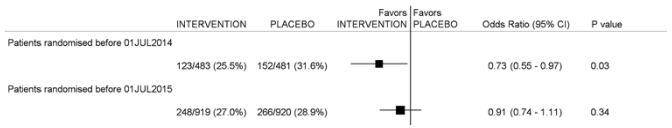
• Annane trial	3.5 years	n=299	19 sites
• CORTICUS	3.5 years	n=499	52 sites
• VASST	5 years	n=778	27 sites
• APROCCHS	6.9 years	n=1241	26 sites
• ADRENAL	4.1 years	n=3800	69 sites

DMC and close to 1st interim analysis



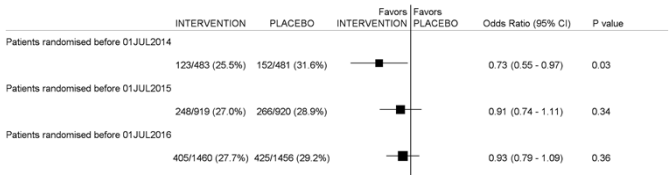
Sample size 950 – approximately CORTICUS X 2 and Annane X 3

As the study progressed….



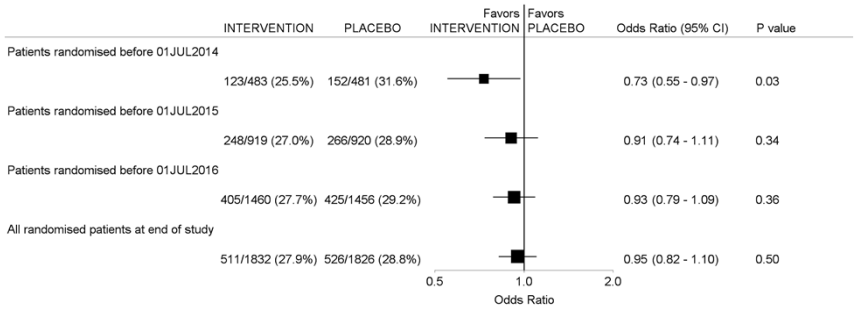
Sample size 1840 – approximately 3.5 X CORTICUS and Annane X 6

DMC and 2nd interim analysis



Sample size 2900 – approximately CORTICUS X 6 and Annane X 10

Study completion



Post hoc-sensitivity analysis – applying Sepsis-3 criteria

Variable	Hydrocortisone (N = 969)	Placebo (N = 968)	Odds Ratio	Lower CI 95%	Upper CI 95%	P-value
Mortality D90						.
Unadjusted	312/963 (32.4%)	337/958 (35.2%)	0.88	0.73	1.07	0.20
Adjusted			0.86	0.70	1.06	0.19
						.
Mortality D28						.
Unadjusted	259/969 (26.7%)	300/968 (31.0%)	0.81	0.67	0.99	0.04
Adjusted			0.80	0.64	0.99	0.06

In conclusion

- The administration of hydrocortisone did not result in lower 90- day mortality than placebo among mechanically ventilated patients with septic shock.
- Some secondary outcomes were better in the hydrocortisone group

NEJM

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- Members of the MC
- NEJM

Australia
- Austin Hospital
- Bendigo Hospital
- Blacktown Hospital
- Calvary Mater Hospital Newcastle
- Footscray Hospital
- Fremantle Hospital / Fiona Stanley Hospital
- Geelong Hospital
- Gold Coast University Hospital
- Gosford Hospital
- Ipswich General Hospital
- John Hunter Hospital
- Liverpool Hospital
- Logan Hospital
- Lyell McEwin Hospital
- Mackay Hospital
- Mater Health Services (Private), Brisbane
- Mater Health Services (Public), Brisbane
- Monash Medical Centre
- Nambour General Hospital
- Nepean Hospital
- Northern Hospital
- Prince Charles Hospital
- Prince of Wales Hospital
- Princess Alexandra Hospital
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- Wollongong Hospital

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- Middlemore Hospital
- North Shore Hospital
- Tauranga Hospital
- Waikato Hospital
- Wellington Hospital

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