THE STEROID STORY

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

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Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

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ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

3800 PATIENTS

69 ICUS

5 COUNTRIES

200MG HYDROCORTISONE VS. PLACEBO

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Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

NO DIFFERENCE IN 90-DAY MORTALITY
27.9% VS 28.8%, OR 0.95

EARLIER SHOCK REVERSAL
FASTER LIBERATION FROM MECHANICAL VENTILATION
EARLIER DISCHARGE FROM ICU
REDUCED FREQUENCY OF BLOOD TRANSFUSION

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ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

1241 PATIENTS

34 FRENCH ICUS

200MG HYDROCORTISONE PLUS FLUDROCORTISONE VS. PLACEBO

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ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

LOWER 90-DAY MORTALITY IN STEROID GROUP: 43 VS. 49.1%, P=0.03

FASTER WEANING OF VENTILATION

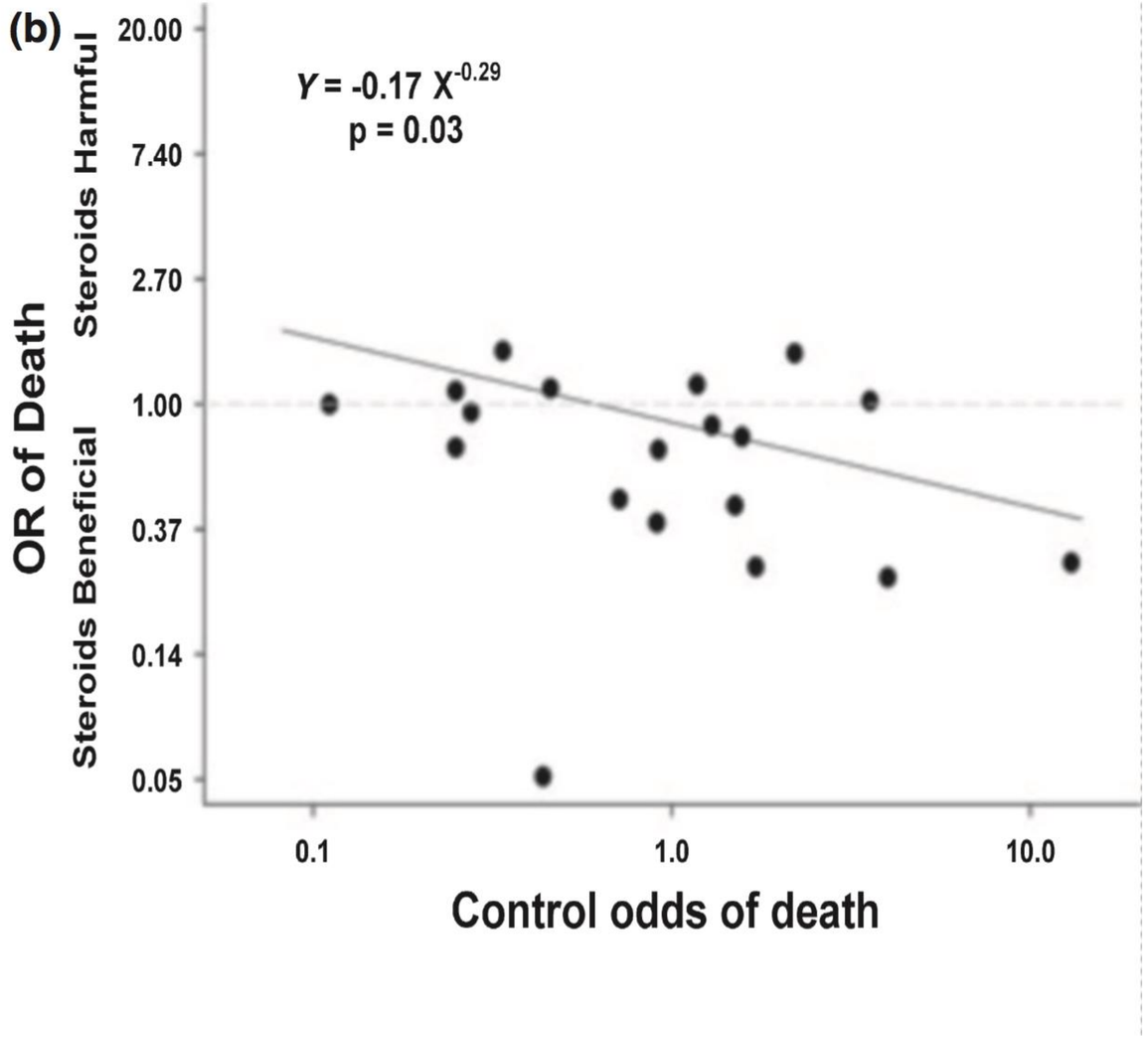
FASTER WEANING OF VASOPRESSORS

MORE DAYS FREE OF ORGAN FAILURE

WERE THE POPULATIONS DIFFERENT?

ADRENAL	APROCCHSS
4 HOURS VASOPRESSORS NO MINIMUM DOSE MECHANICAL VENTILATION	6 HOURS VASOPRESSORS MINIMUM DOSE .025 MCG/KG/MIN MINIMUM SOFA SCORE
MEDICAL 68% BACTERAEMIA 34%	MEDICAL 80% BACTERAEMIA 36%
MEAN LACTATE 3.8 MMOL/L RRT 12.3%	MEAN LACTATE 4.4 MMOL/L RRT 28.1%
PLACEBO MORTALITY 28.8%	PLACEBO MORTALITY 49.1%

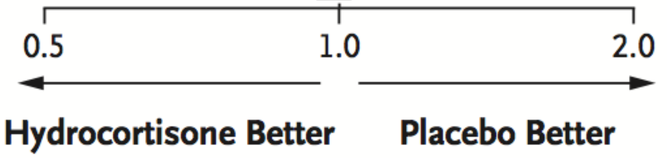
INFLUENCE OF SEVERITY OF ILLNESS ON STEROID RES



Minneci et al, 2009

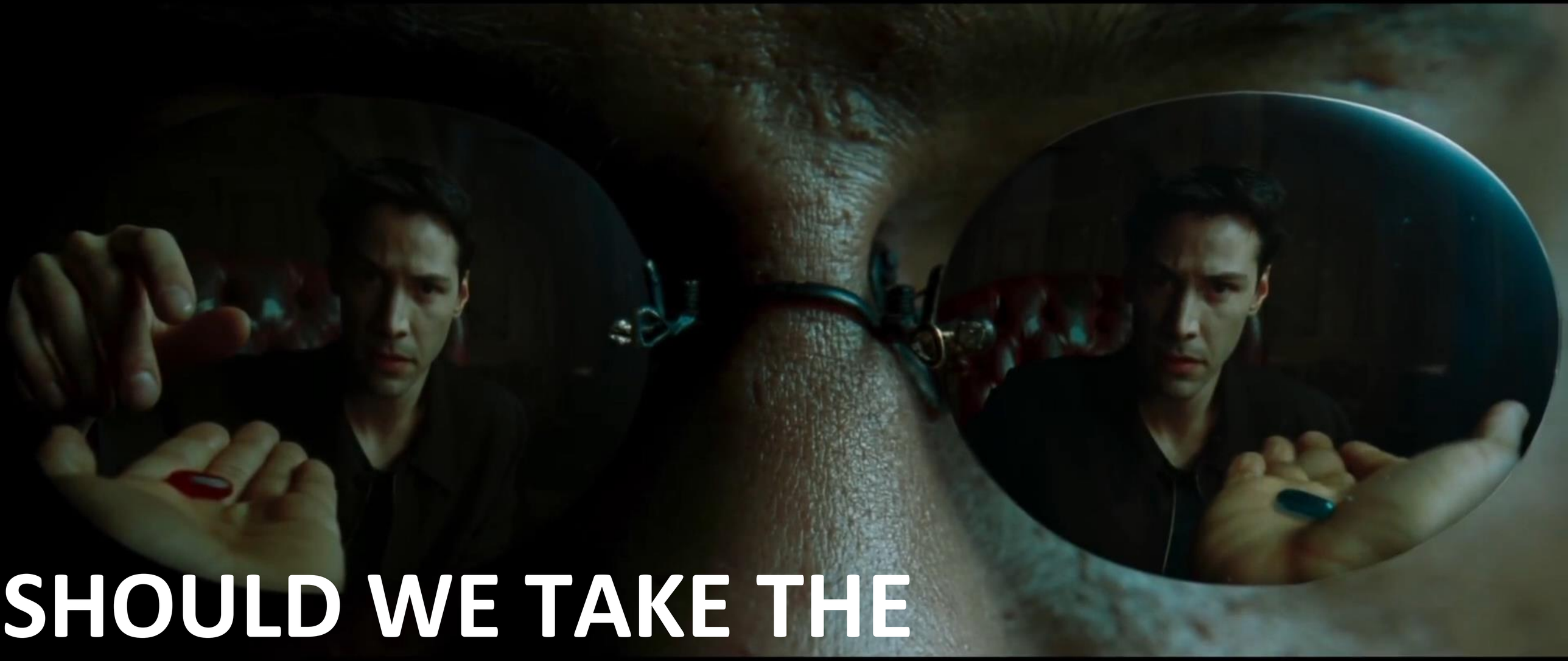
B **Subgroup Analysis of Death at 90 Days**

Subgroup	Hydrocortisone	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	

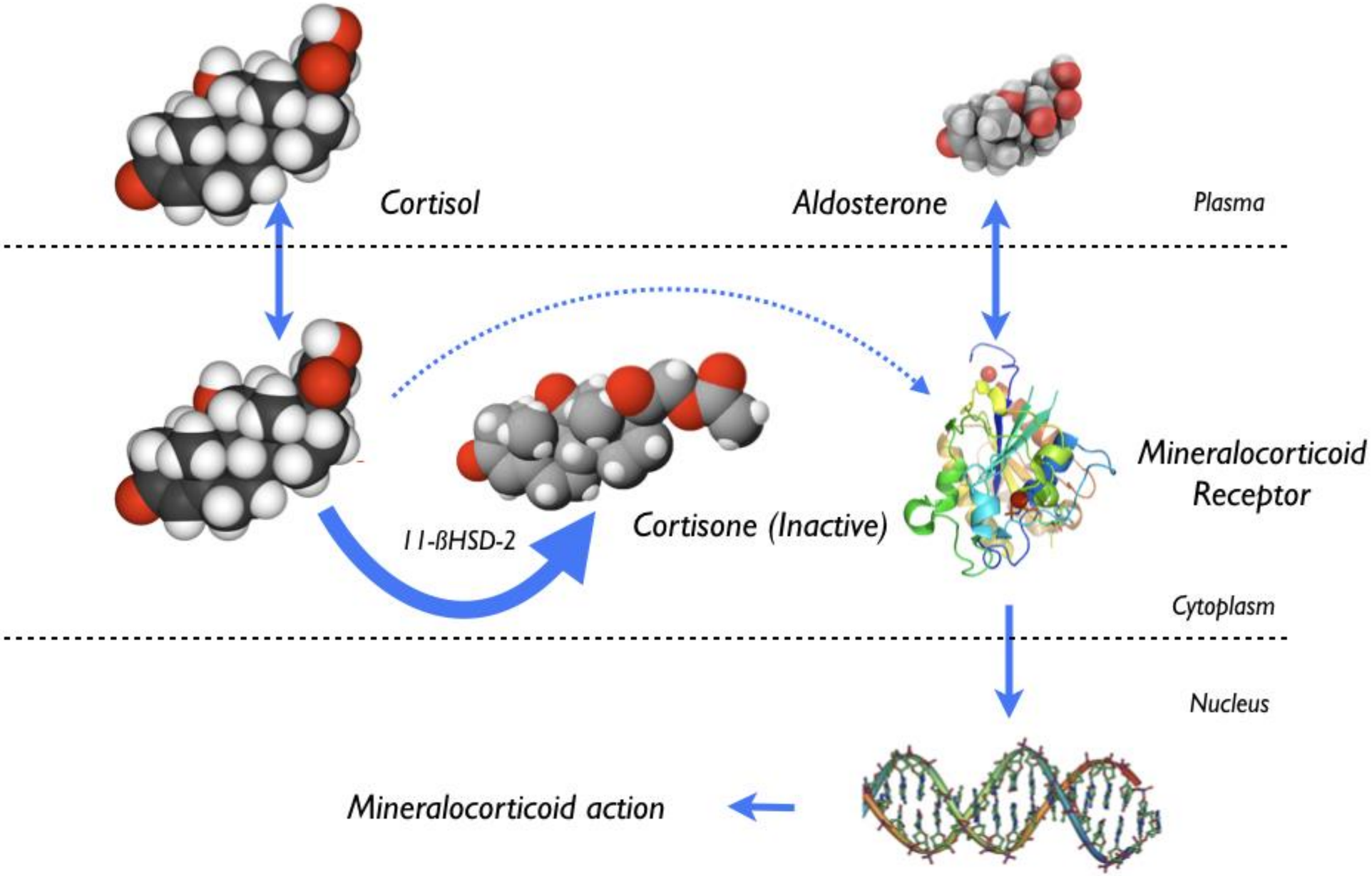


POST-HOC SENSITIVITY ANALYSIS APPLYING APROCCHSS INCLUSION

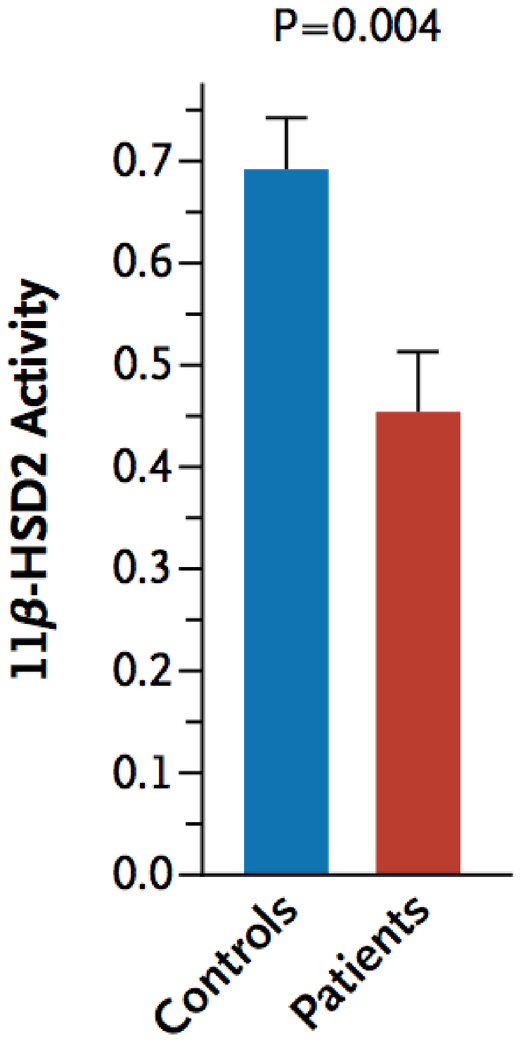
	HYDROCORTISONE (N=454)	PLACEBO (N=449)	
MORTALITY D90 UNADJUSTED	187/453 (41.3%)	200/445 (44.9%)	OR =0.86 (0.66-1.12, P=0.27)
ADJUSTED			OR =0.84 (0.6-1.1, P=0.33)
MORTALITY D28 UNADJUSTED	166/454 (36.6%)	184/449 (40.3%)	OR =0.85 (0.65-1.12, P=0.25)
ADJUSTED			OR =0.84 (0.62-1.13, P=0.28)



SHOULD WE TAKE THE FLUDROCORTISONE?


Cortisol
Aldosterone
Plasma
11-ßHSD-2
Cortisone (Inactive)
Mineralocorticoid
Receptor
Cytoplasm
Nucleus
Mineralocorticoid action

C



Boonen et al, NEJM 2016

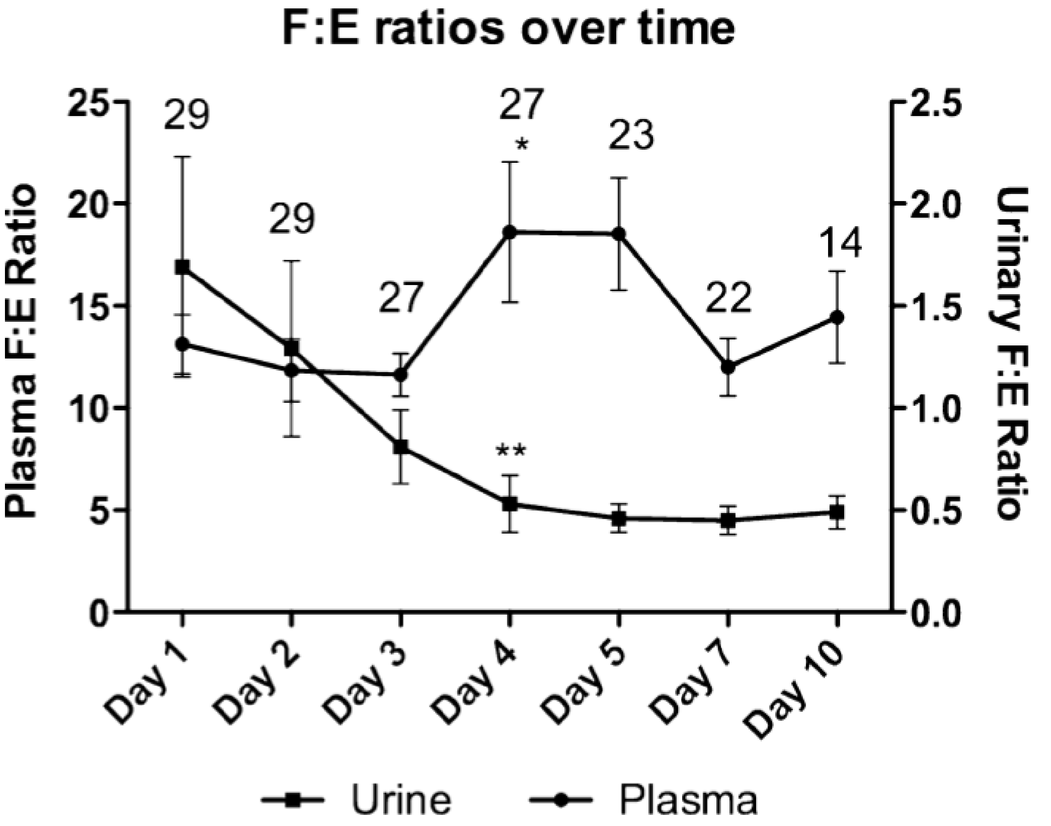


FIG. 3. **Changes in plasma (circles) and urine (squares) F:E ratio over the study period**. Error bars indicate SEM. The numbers above each data point indicate the remaining number of patients in the study. *P = 0.02 compared with day 1; **P = 0.002 compared with day 1.

Cohen et al, SHOCK 2011

DOES ROUTE OF ADMINISTRATION MATTER?

Research

Open Access

Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial

Pekka Loisa[1], Ilkka Parviainen[2], Jyrki Tenhunen[3], Seppo Hovilehto[4] and Esko Ruokonen[2]

Glycemic control in study groups

	Bolus group ($n = 23$)	Infusion group ($n = 22$)	p value
Mean blood glucose (mmol/l)	6.4 ± 0.7	6.2 ± 0.7	0.040
Blood glucose variation coefficient (percentage)	20.2 ± 6.9	16.5 ± 4.8	0.063
Blood glucose > 7 mmol/l (episodes per patient)	15.7 ± 8.5	10.5 ± 8.6	0.039
Blood glucose > 8.3 mmol/l (episodes per patient)	3.6 ± 3.4	2.6 ± 3.2	0.383

Hemodynamic parameters in study groups

	Day 1	Day 2	Day 3	Day 4	Day 5	p value
Shock reversal, n (percentage)						
Bolus group	0/24 (0%)	3/24 (13%)	14/24 (58%)	18/24 (75%)	20/24 (83%)	0.48
Infusion group	0/24 (0%)	5/24 (21%)	12/24 (50%)	14/24 (58%)	15/24 (63%)	

Observational Study

Timing, method and discontinuation of hydrocortisone administration for septic shock patients

Miguel A Ibarra-Estrada, Quetzalcóatl Chávez-Peña, Claudia I Reynoso-Estrella, Jorge Rios-Zermeño, Pável E Aguilera-González, Miguel A García-Soto, Guadalupe Aguirre-Avalos

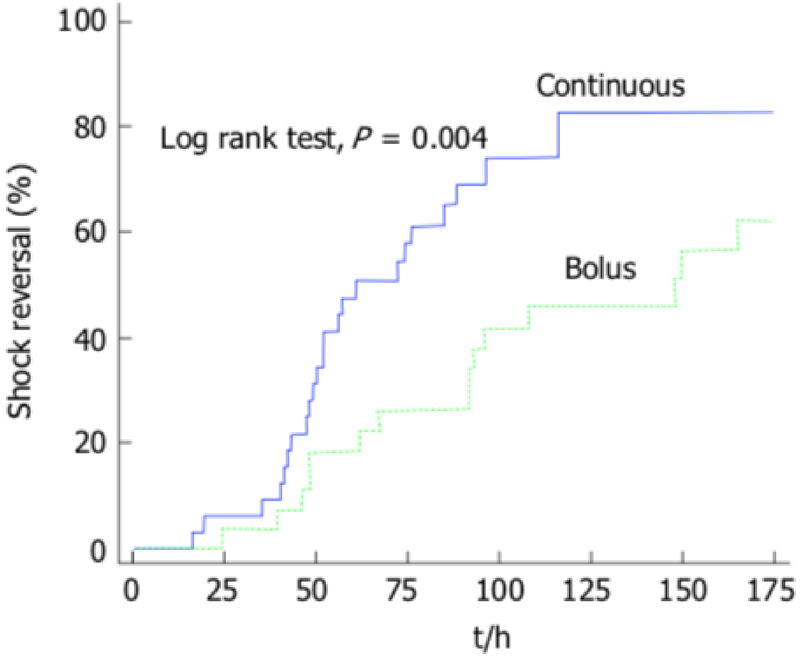


Figure 2 Kaplan-Meier analysis comparing the rate of septic shock reversal, according to administration of hydrocortisone. At 7 d (168 h), 83% of continuous infusion patients were vasopressor-free compared to 63% of patients who were in the bolus administration group, $P = 0.004$.

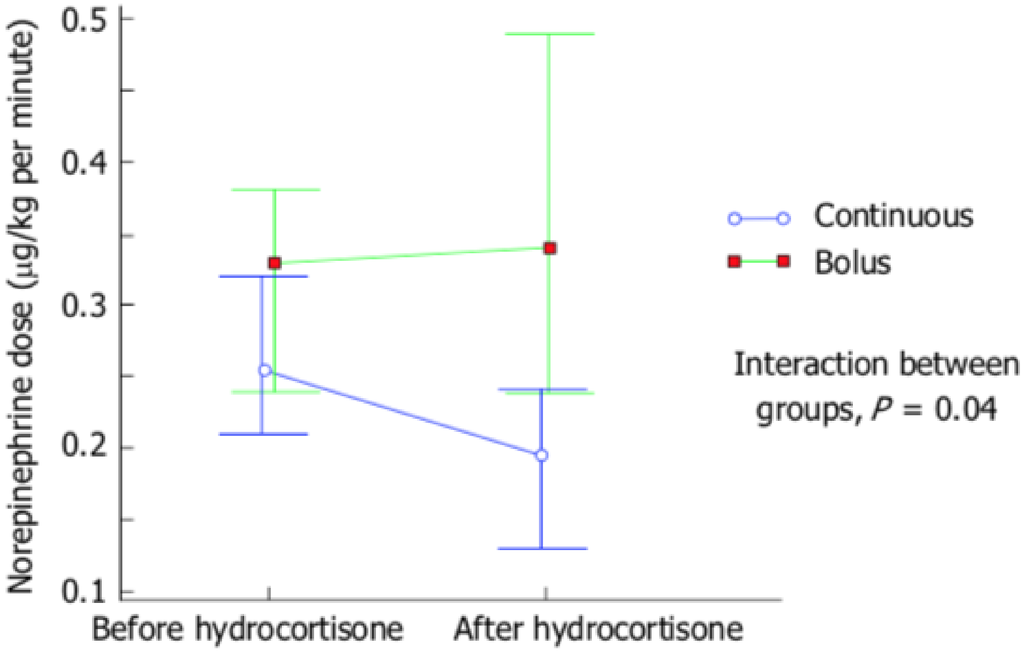


Figure 1 Change in maximal norepinephrine dose from 12 h after initiation of hydrocortisone. Comparison between continuous and bolus administration groups, with two-way mixed ANOVA test, $P = 0.04$.

WHERE WAS THE ETOMIDATE?

ETOMIDATE USE IN THE MAJOR STEROID TRIALS OF SEPTI

	ANNANE 2002	CORTICUS	ADRENAL	APROCCHSS
ETOMIDATE AN EXCLUSION CRITERIA ?	NO (YES AFTER AMENDMENT)	NO	YES	NO
PROPORTION PATIENTS RECEIVING	19%	28%	1.3%	?
DISTRIBUTION	NOT SPECIFIED	29% VS. 26%	1.3% VS 1.2%	?

1

2

3

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

METHODS

In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

RESULTS

Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure–free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

CONCLUSIONS

In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Annane at Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, 104 Blvd. Raymond Poincaré, 92380 Garches, France, or at djillali.annane@aphp.fr.

*A complete list of investigators in the APROCCHSS trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2018;378:809-18.
DOI: 10.1056/NEJMoa1705716

action between the treatment group and the Sepsis-3 criteria (P=0.42). Likewise, the patients' response to glucocorticoids did not vary according to the baseline dose of vasopressor (P=0.65 for interaction).

In response to Arafah: none of the patients in the APROCCHSS trial received etomidate at any time before or after randomization. It may be speculative to rule out any benefit for the addition of fludrocortisone to hydrocortisone when two independent trials showed a significant reduction in mortality with the combination of these two drugs.[3]

Gunst and Van den Berghe contend that fludrocortisone had no added value, since 200 mg of hydrocortisone would saturate the mineralocorticoid receptor. However, the exact roles of the mineralocorticoid receptor in epithelial and nonepithelial tissues, regardless of whether they are "protected" by 11β-hydroxysteroid dehydrogenase type 2, remain unclear.[4] The binding of the mineralocorticoid receptor by aldosterone (or fludrocortisone) or by cortisol (or hydrocortisone) may result in different downstream signaling, and cortisol variably behaves as an agonist or an antagonist to the mineralocorticoid receptor. The added value of fludrocortisone has been suggested in experimental endotoxemia.[2] The evaluation of a survival benefit for glucocorticoids among patients who do not have a response to corticotropin testing was the primary analysis of the Ger-Inf-05 trial[3] and a secondary analysis in the APROCCHSS trial. In addition, the adrenal status was not available for 232 of 614 patients (37.8%) in the glucocorticoid group and 229 of 627 patients (36.5%) in the placebo group, which further reduced the power of the APROCCHSS trial to test for an interaction between trial group and adrenal status.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 2010;303:341-8.
2. Laviolle B, Nesseler N, Massart C, Bellissant E. Fludrocortisone and hydrocortisone, alone or in combination, on in vivo hemodynamics and in vitro vascular reactivity in normal and endotoxemic rats: a randomized factorial design study. J Cardiovasc Pharmacol 2014;63:488-96.
3. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
4. Funder JW. Aldosterone and mineralocorticoid receptors-physiology and pathophysiology. Int J Mol Sci 2017;18:E1032.

DOI: 10.1056/NEJMc1804993


TIME FOR A META ANALYSIS!!

META ANALYSES SINCE PUBLICATION OF ADRENAL & APROCCHSS

- Relative Risk Short Term Mortality with Corticosteroids vs Placebo:
  - RR 0.98 (95% CI 0.89 - 1.08, p=0.71)
  - Conclusion: Short term mortality unaffected.

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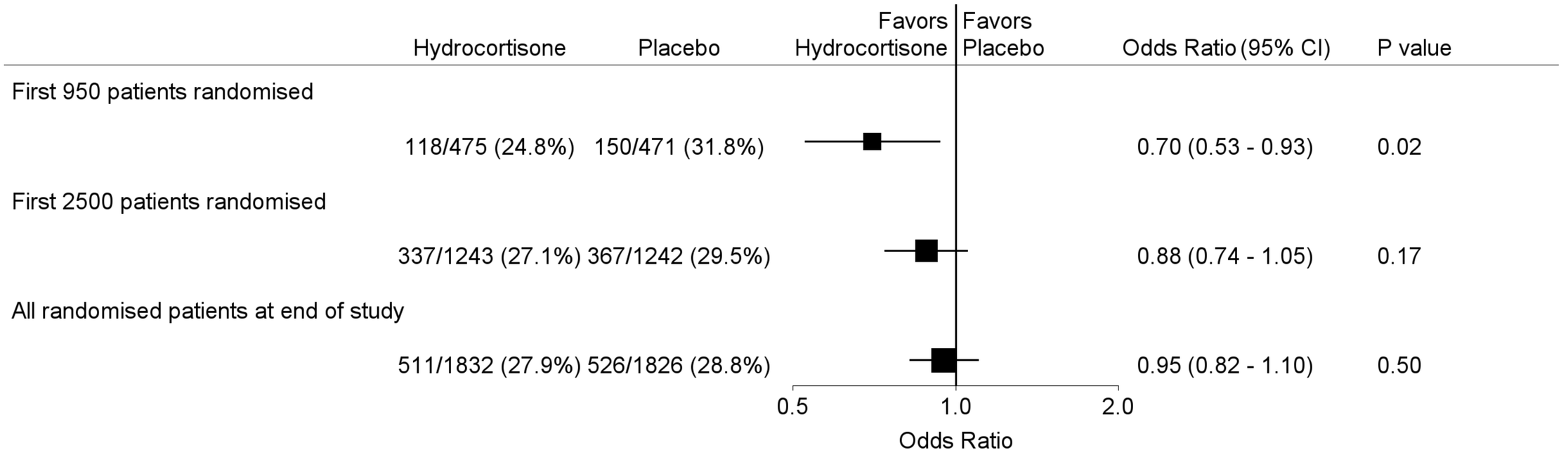
  - Conclusion: Short term mortality unaffected.

  - RR 0.93 (95% CI 0.84 - 1.03)
  - Conclusion: “Small reduction or no reduction in mortality”


IS IT ALL JUST CHANCE?

ADRENAL INTERIM ANALYSES



PRACTICE RECOMMENDATIONS

- HC - ROLE IN IMPROVING MORTALITY UNCLEAR
- EVIDENCE OF BENEFIT - PATIENT-CENTRED SECONDARY OUTCOMES
- HYDROCORTISONE PRESCRIBED IN A DOSE OF 200MG/DAY.
- NO THRESHOLD DOSE OF VASOPRESSORS/SICKNESS
- RECOMMENDED DURATION - 7 DAYS, EITHER INFUSION OR BOLUS.
- NO REQUIREMENT FOR DOSE TAPERING.
- NO REQUIREMENT TO PERFORM A CORTICOTROPHIN TEST
- ADDITIONAL FLUDROCORTISONE IS NOT NECESSARY