



GLUCOCORTICOIDS FOR SEPSIS SHOULD I USE THEM WITH FLUDROCORTISONE

Djillali Annane

Raymond Poincare hospital, Garches

Dean of Faculty of Health Science Simone Veil,

University of Versailles, University Paris Saclay

CONFLICT OF INTEREST

- All research programs, including APROCCHSS trial, were publicly funded (French Ministry of Health, EC)
- Academic COI: chair of ESICM/SCCM TF for 2018 Guidelines on CIRCI, member of SSC guidelines panel for 2008, 2012 & 2016 revisions
- All data from APROCCHSS presented in this slide-show are available @nejm.org

The left side of the slide features a series of vertical bars of varying widths and shades of gray, ranging from light to dark. Below these bars are several white circles of different sizes, arranged in a descending staircase pattern from top-left to bottom-right. The largest circle is positioned at the top left, with smaller circles following it down and to the right.

● WHY I GIVE STEROIDS?

Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)

Djillali Annane, MD, PhD¹; Stephen M. Pastores, MD, FCCM²; Wiebke Arlt, MD, DSc, FRCP³; Robert A. Balk, MD, MCCM⁴; Albertus Beishuizen, MD, PhD⁵; Josef Briegel, MD, PhD⁶; Joseph Carcillo, MD, FCCM⁷; Mirjam Christ-Crain, MD, PhD⁸; Mark S. Cooper, MD⁹; Paul E. Marik, MD, FCCM¹⁰; Gianfranco Umberto Meduri, MD¹¹; Keith M. Olsen, PharmD, FCCM¹²; Bram Rochweg, MD¹³; Sophia C. Rodgers, RN, MSN, ACNP, FCCM¹⁴; James A. Russell, MD¹⁵; Greet Van den Berghe, MD, PhD¹⁶

DEFINITION OF CIRCI

Defined as dysregulated host response to acute inflammation:

- inadequate cellular corticosteroid activity
- for the severity of critical illness,
- manifested by insufficient GC–GR -mediated down-regulation of pro-inflammatory transcription factors.



Comparison

Corticosteroid therapy

Intravenous corticosteroids plus usual care



or

No corticosteroid therapy

Usual care only



Corticosteroids

No corticosteroids

Strong

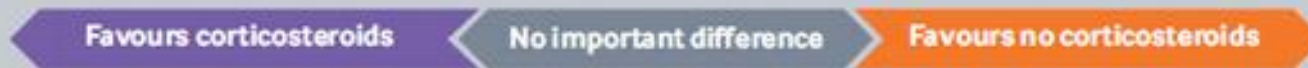
Weak

Weak

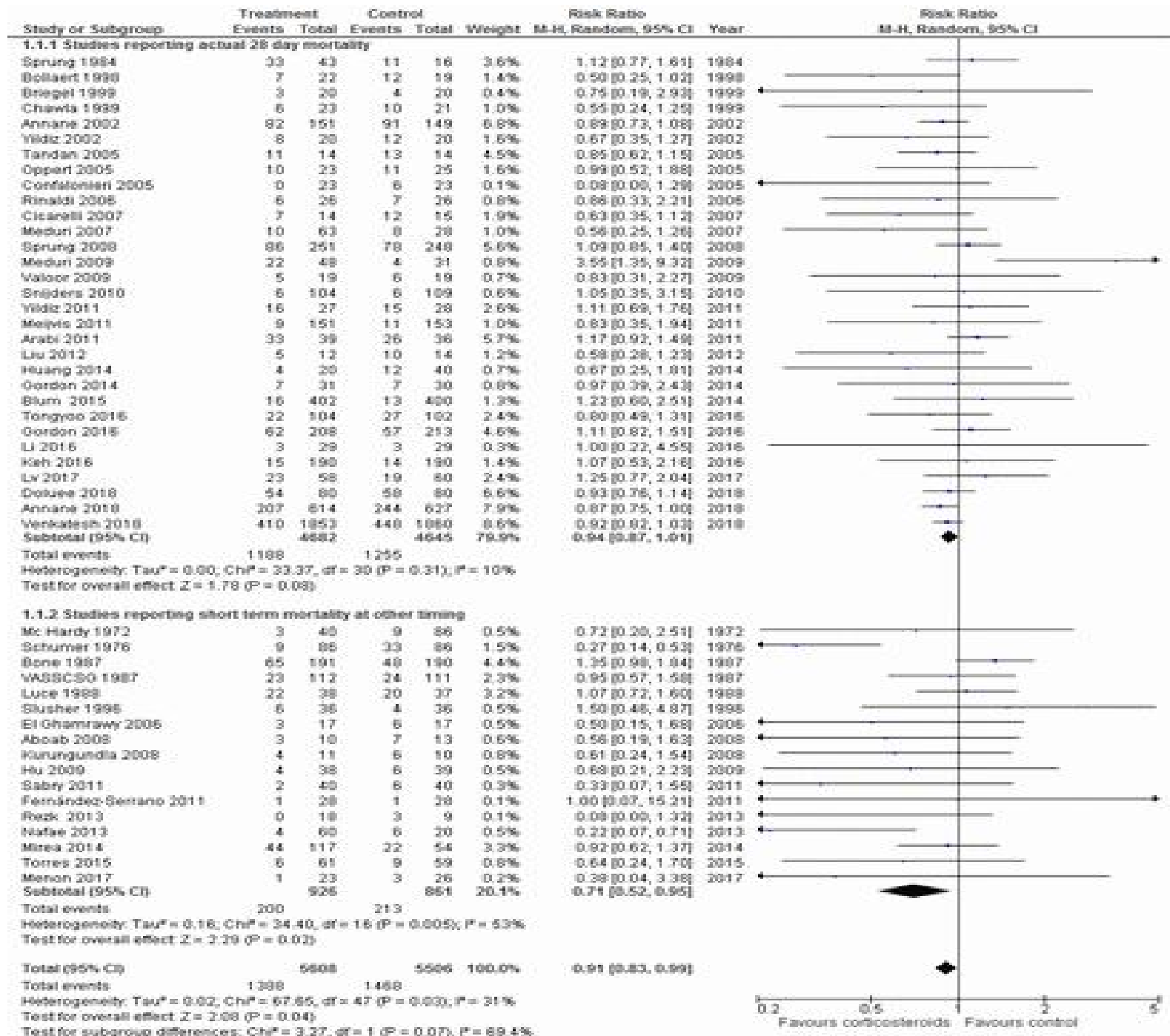
Strong

We suggest corticosteroid therapy rather than no corticosteroid therapy.
Either option is reasonable.

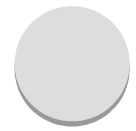
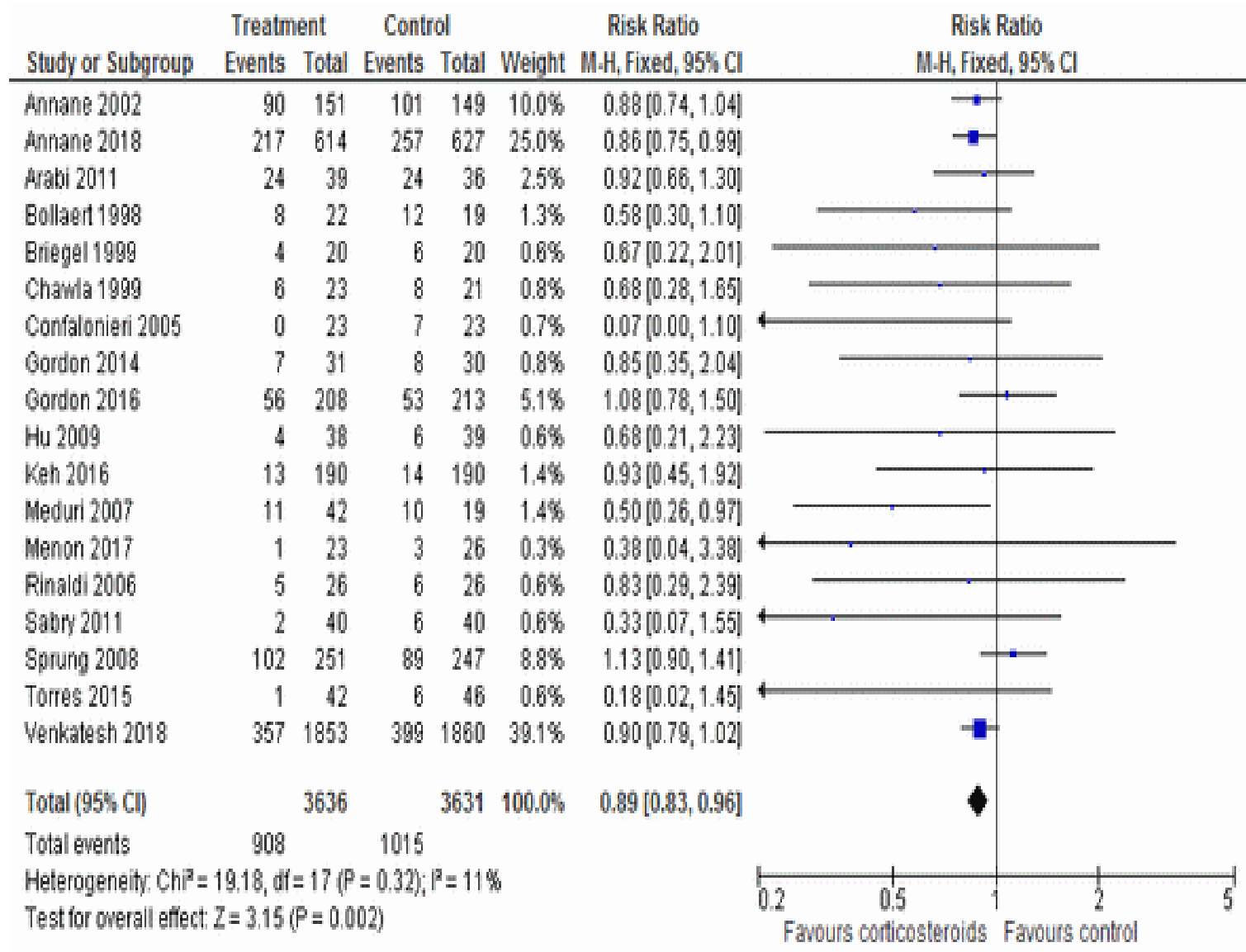
Comparison of benefits and harms



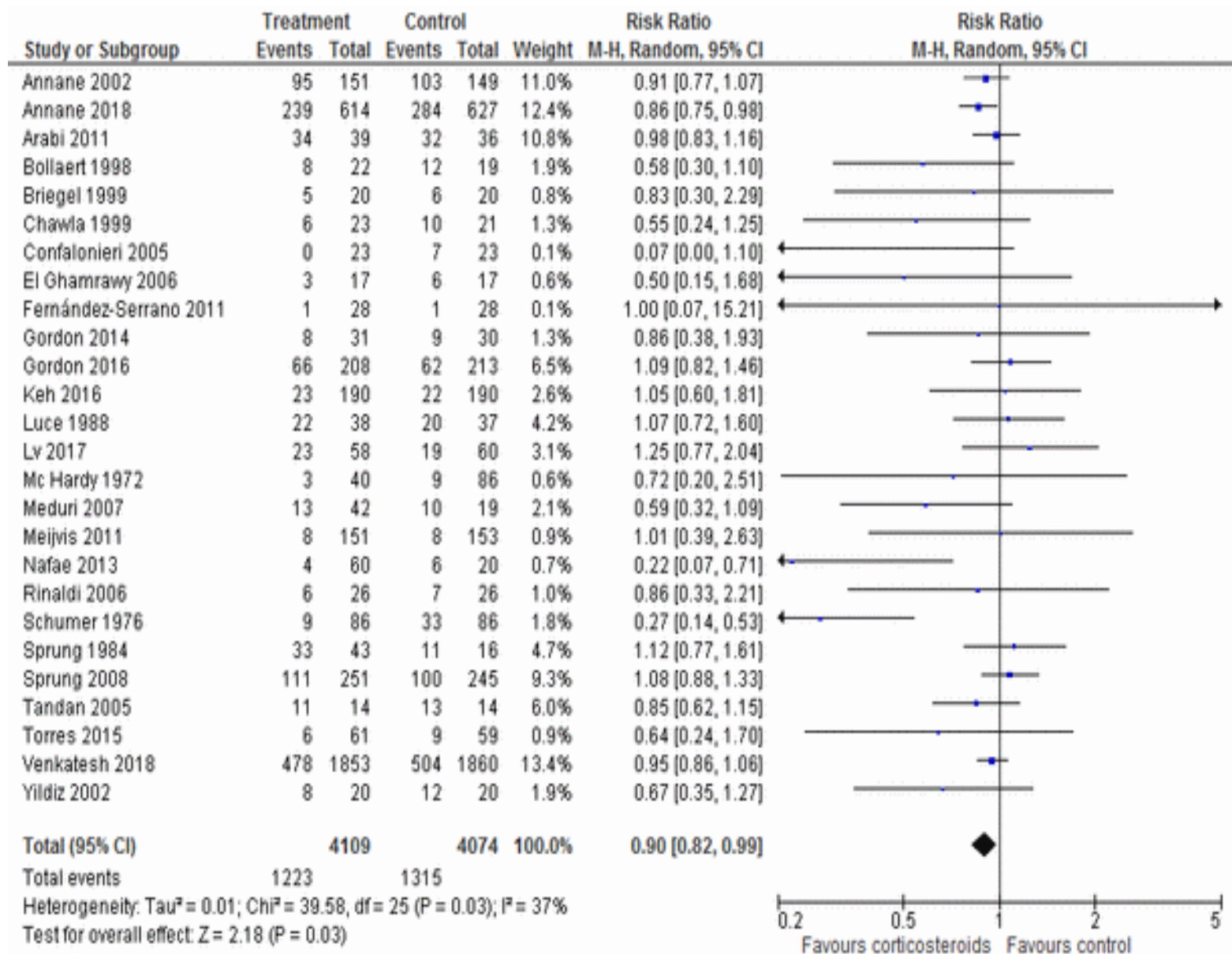
	Events per 1000 people		Evidence quality
Mortality	236	18 fewer	★★★★ Low
Neuromuscular weakness	303	53 fewer	★★★★ Low
Quality of Life	Unknown		★★★★ None
Stroke	10	No important difference	★★★★ Very low
Myocardial infarction	27	No important difference	★★★★ Very Low
	Mean number of days		
Length of ICU stay	12.4	0.7 fewer	★★★★ Moderate
Length of hospital stay	31.3	0.7 fewer	★★★★ Moderate



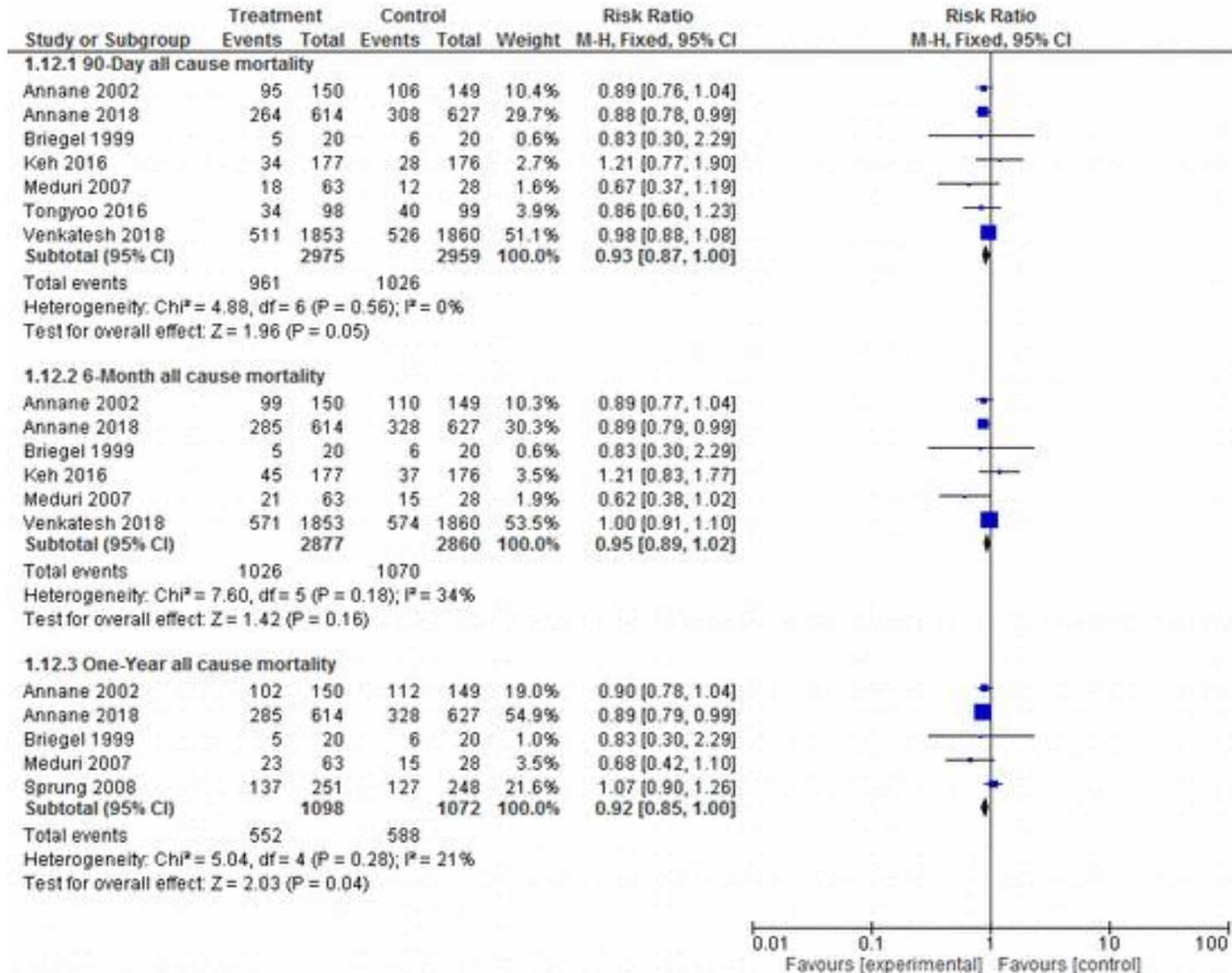
ICU MORTALITY



HOSPITAL MORTALITY



LONG TERM MORTALITY



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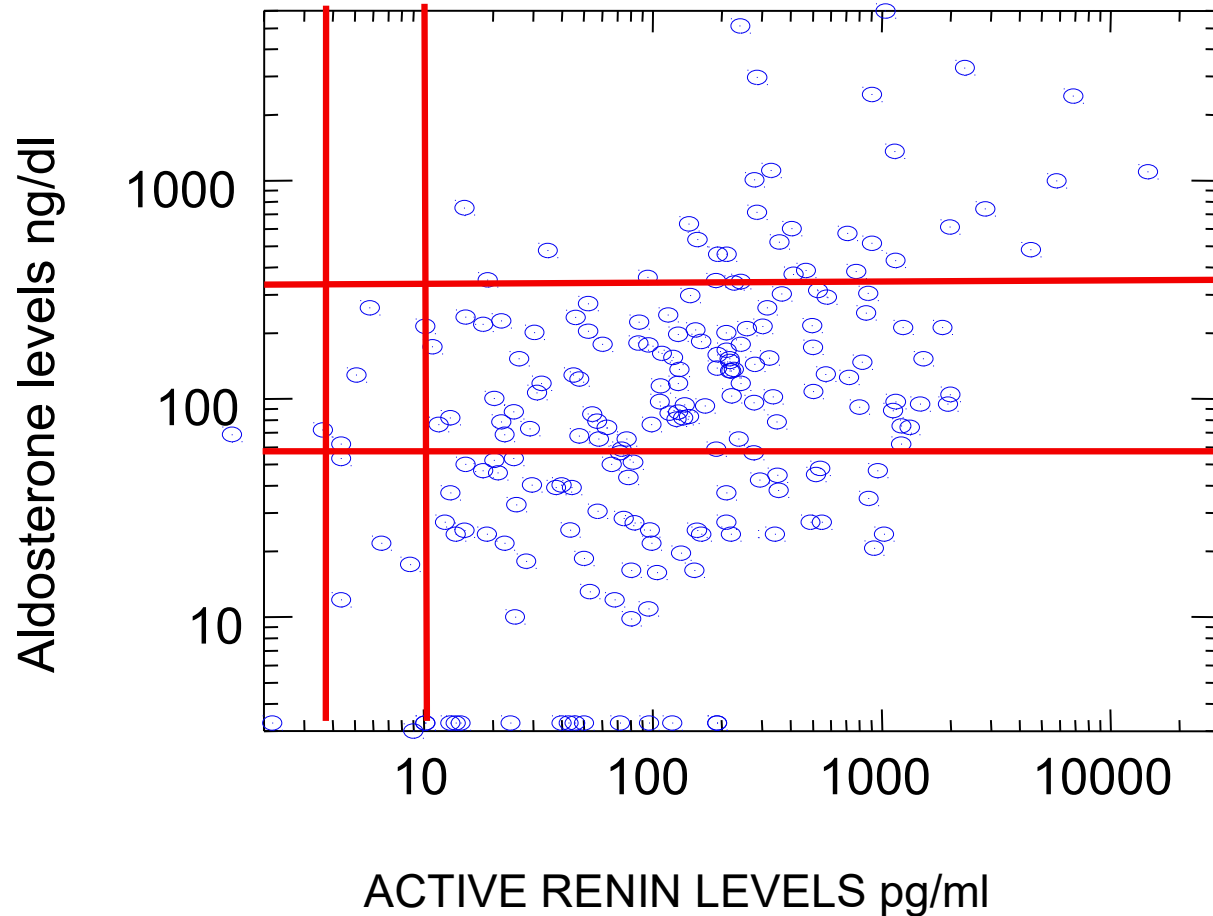
HOW I GIVE STEROIDS?

ROLE OF FLUDROCORTISONE

ALL CORTICOSTEROIDS ARE NOT EQUIVALENT

Molecules	Glucocorticoid activity relative to hydrocortisone	Mineralocorticoid activity relative to hydrocortisone	Non-genomic effects relative to hydrocortisone
Hydrocortisone	1	1	1
Prednisone	4	0.8	4
Prednisolone	4	0.8	4
Methylprednisolone	5	0.5	14
Betamethasone	25	0	20
Dexamethasone	25	0	20
Fludrocortisone	10	125	2

Mineralocorticoid Insufficiency in Septic Shock



N= 225

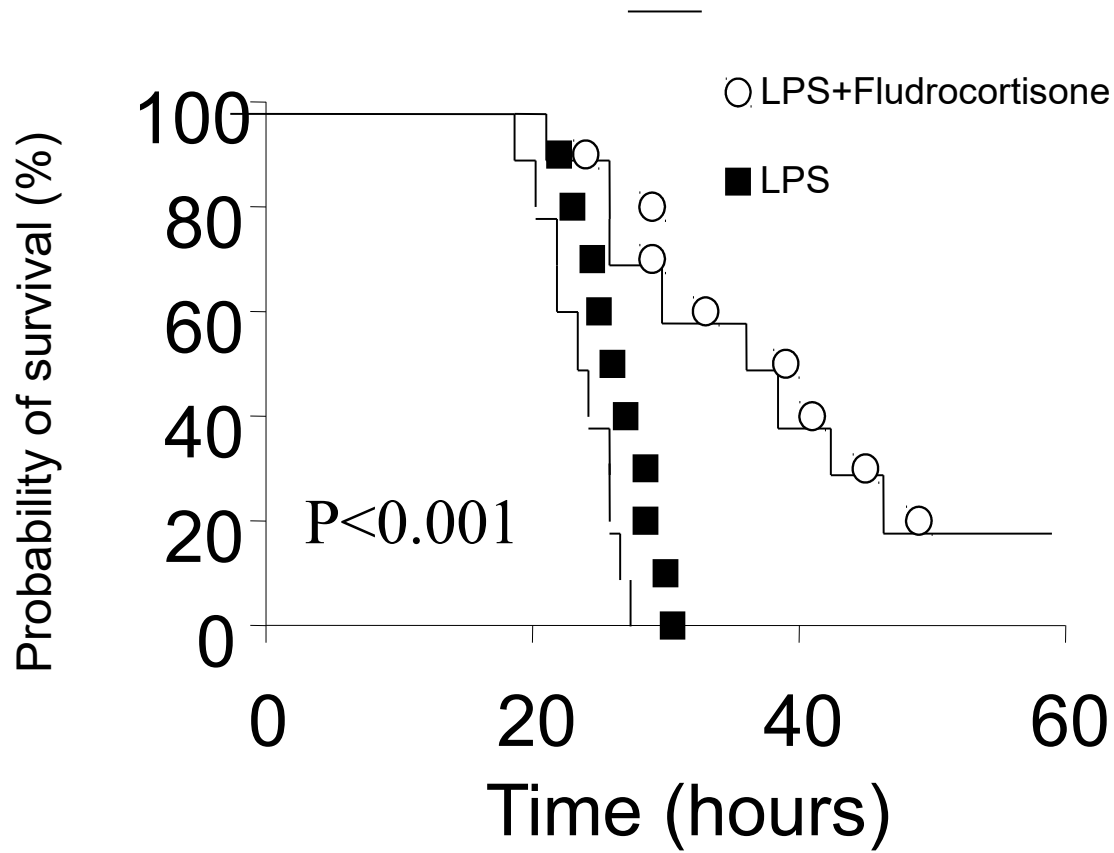


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EXPERIMENTAL DATA

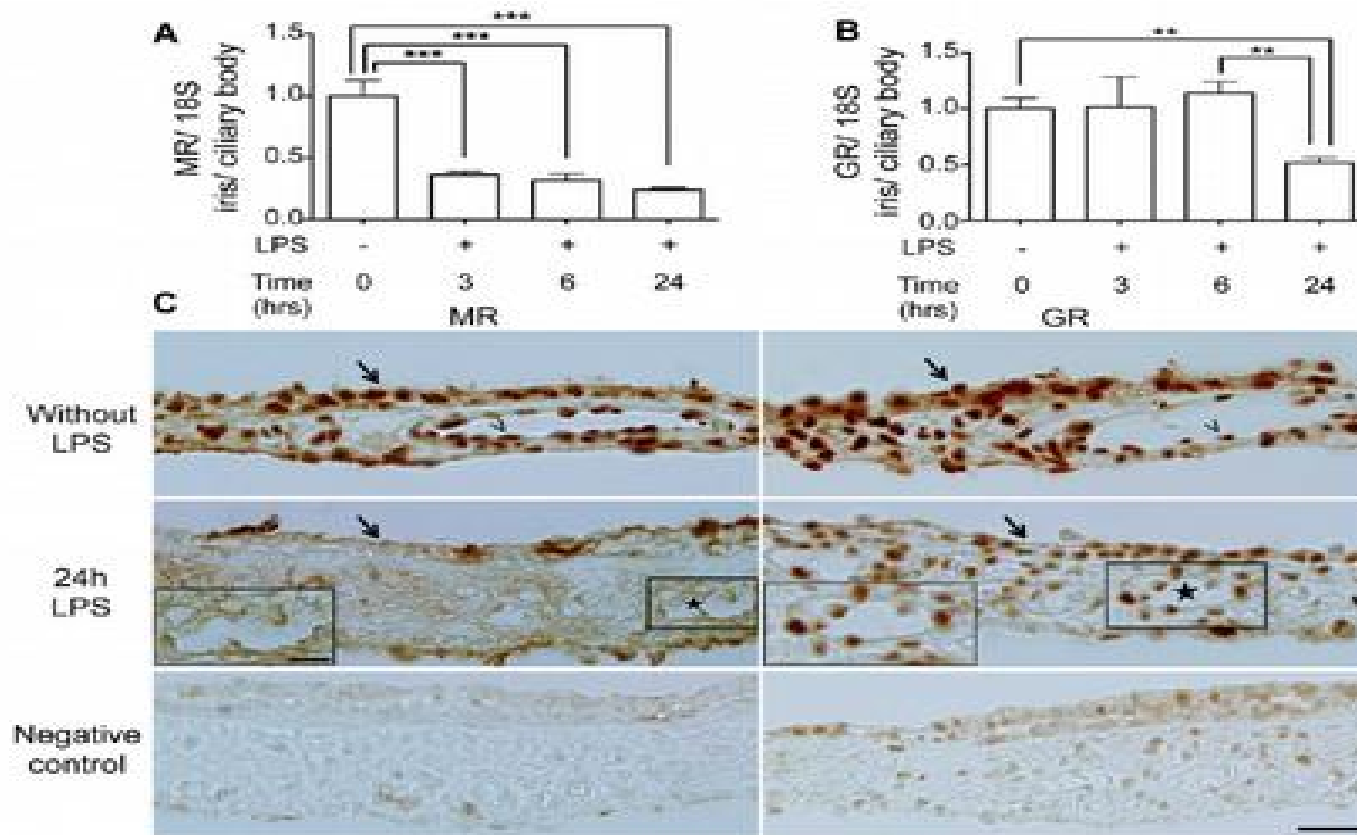
ROLE OF FLUDROCORTISONE

IN SMALL ANIMALS



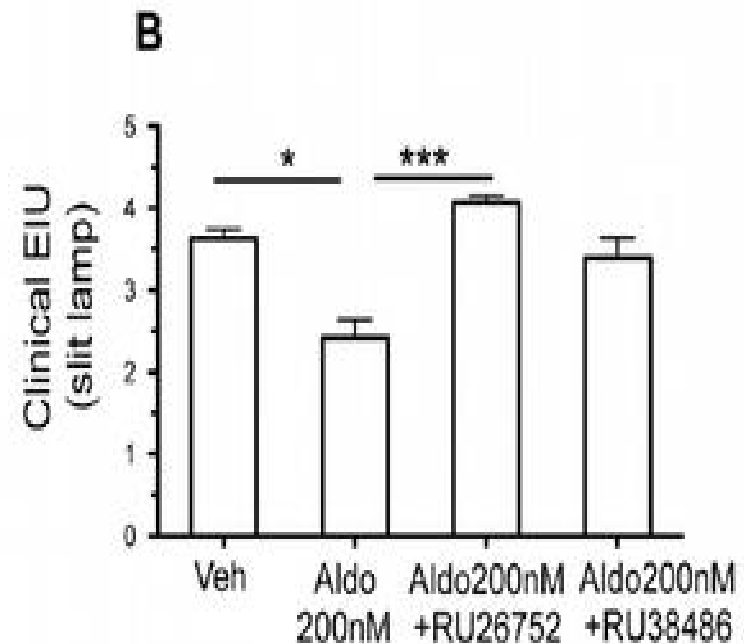
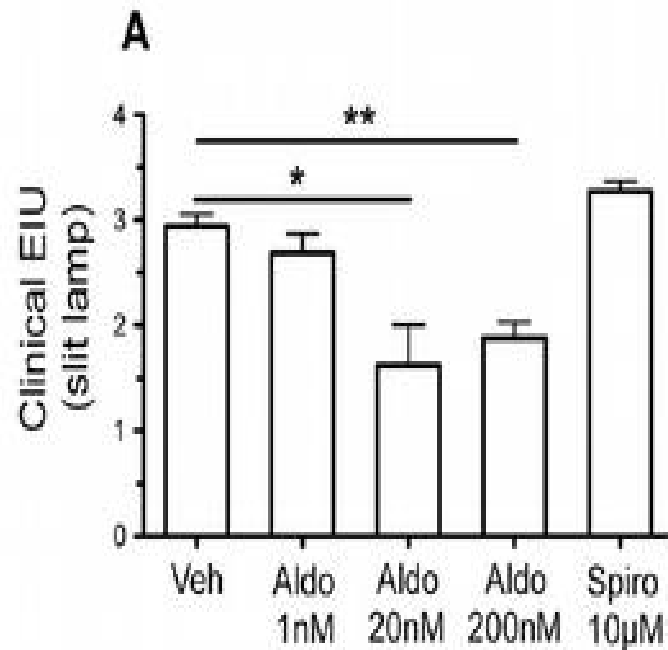
ANTI-INFLAMMATORY EFFECTS OF ALDOSTERONE IN UVEITIS

Aldosterone/Mineralocorticoid Receptor in U



ANIT-INFLAMMATORY EFFECTS OF ALDOSTERONE IN UVEITIS

Aldosterone/Mineralocorticoid Receptor in Uveitis



MC IMMUNE EFFECTS IN SEPSIS

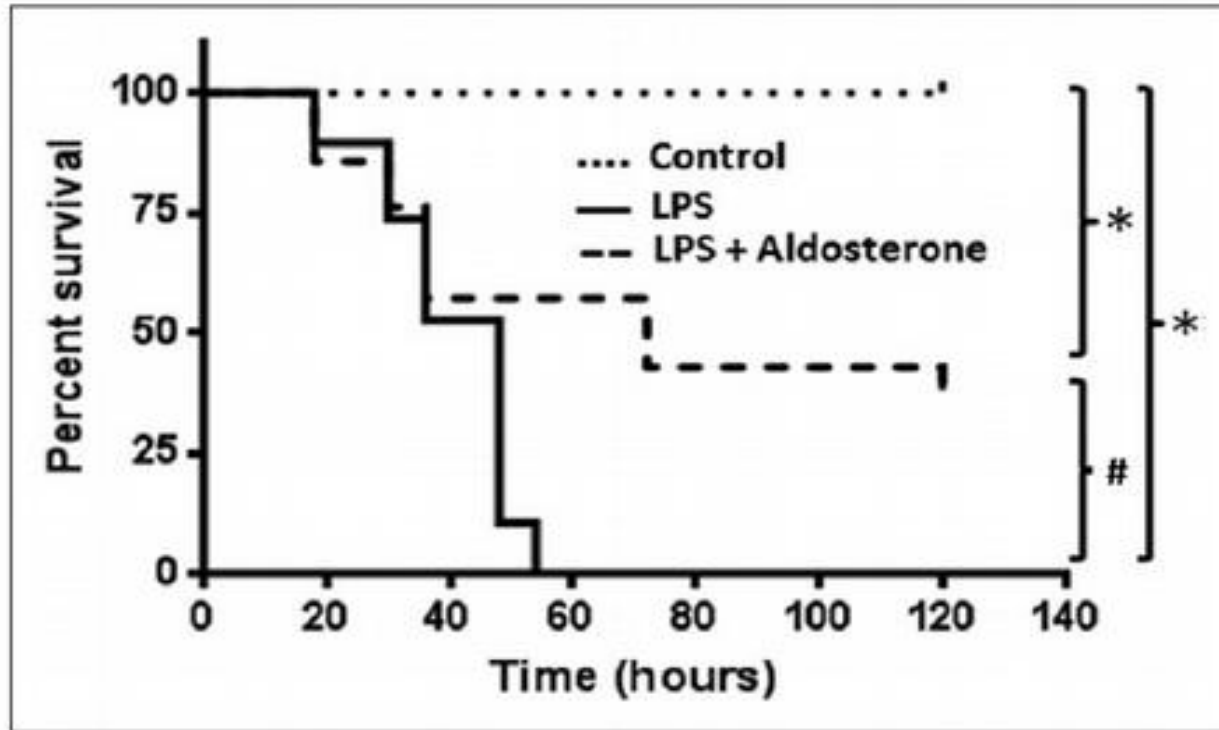
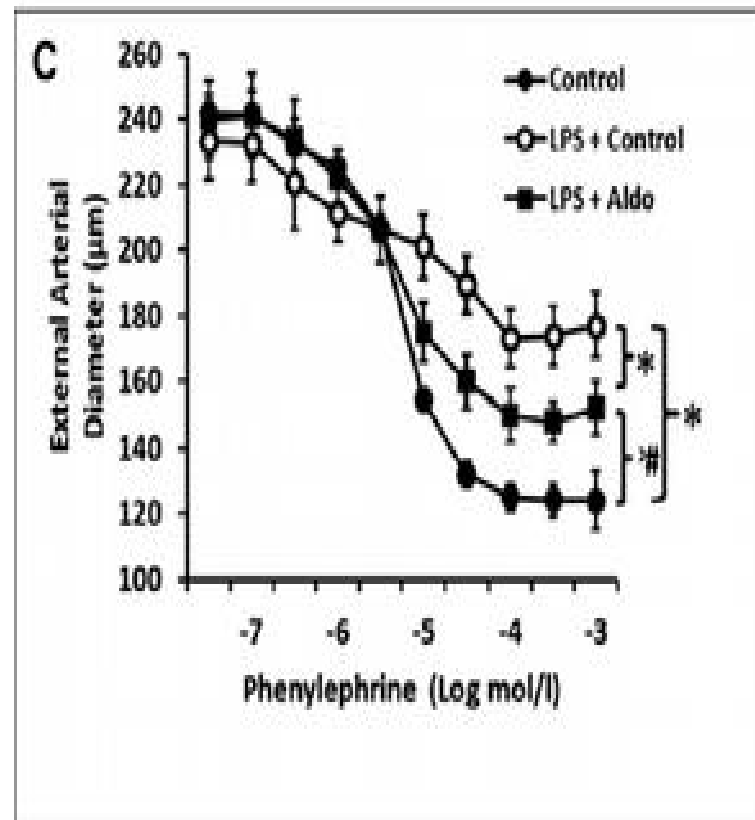
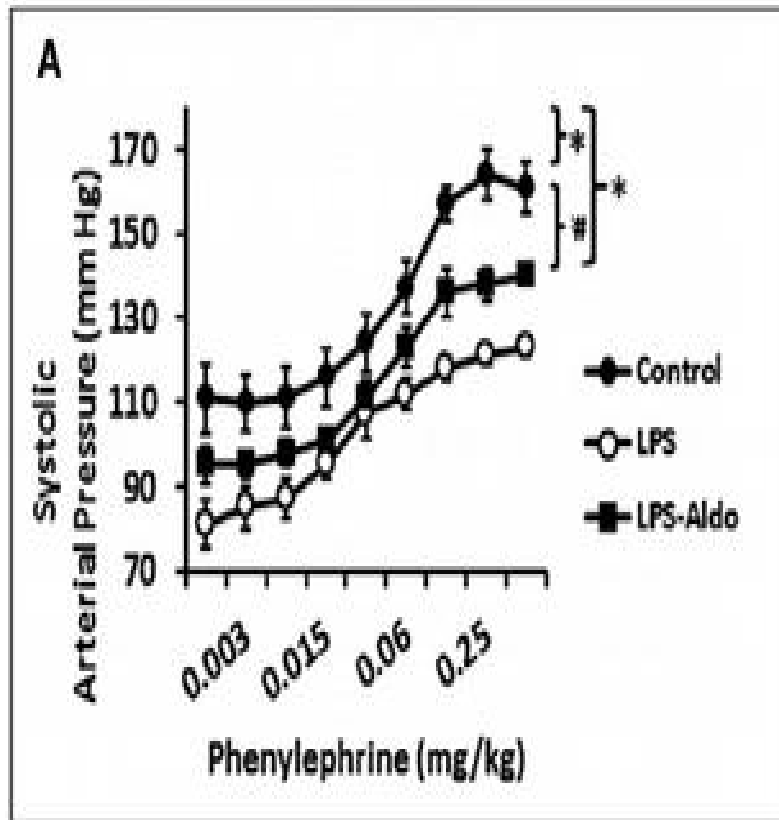
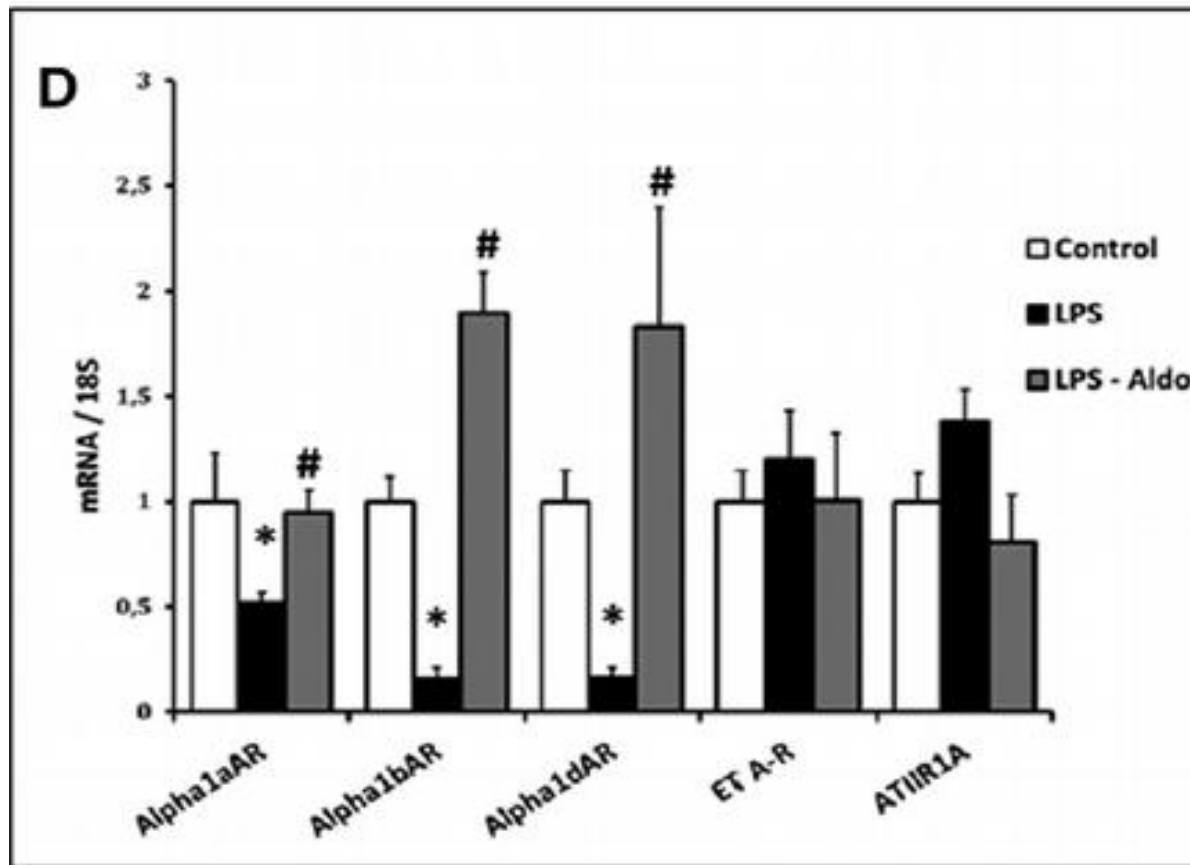


Figure 1. Effects of aldosterone on survival during endotoxic shock—mice were injected intraperitoneally with vehicle or lipopolysaccharide (LPS) (15 mg/kg) with or without aldosterone (1 mg/kg). Survival was monitored for 120 hs * $p < 0.05$ vs control, # $p \leq 0.05$ vs LPS, $n = 20$ in all groups).

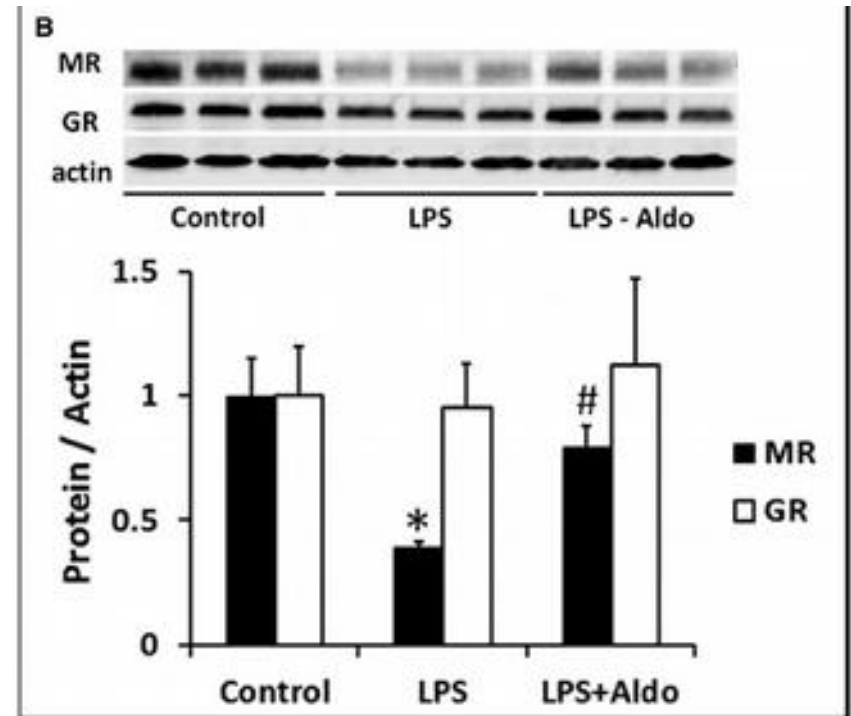
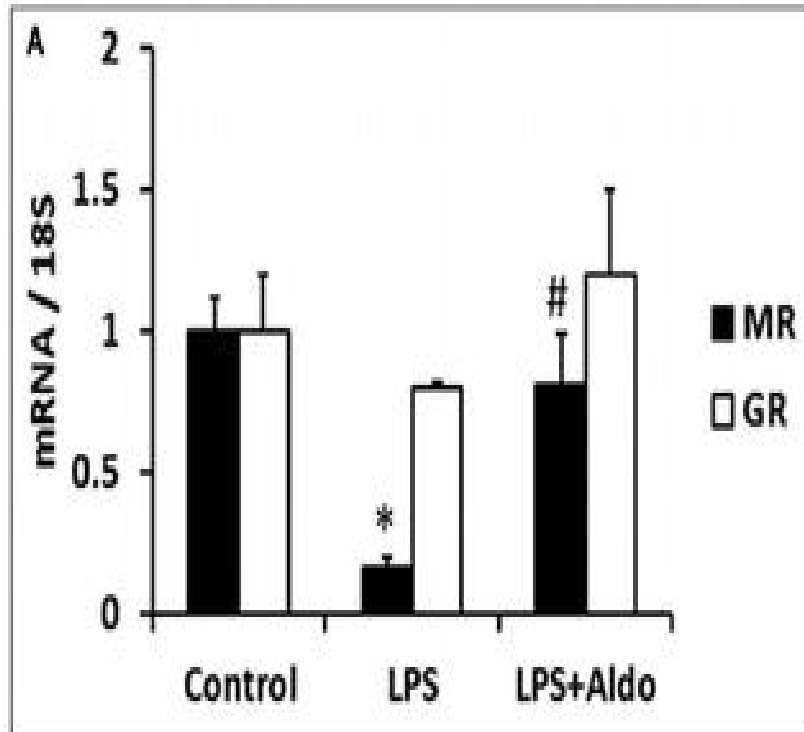
MC IMMUNE EFFECTS IN SEPSIS



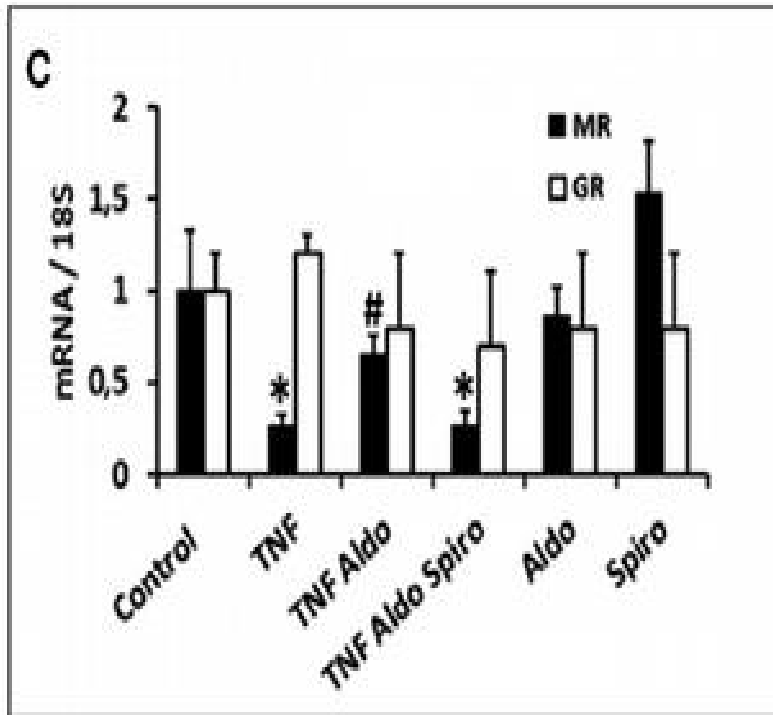
MC IMMUNE EFFECTS IN SEPSIS



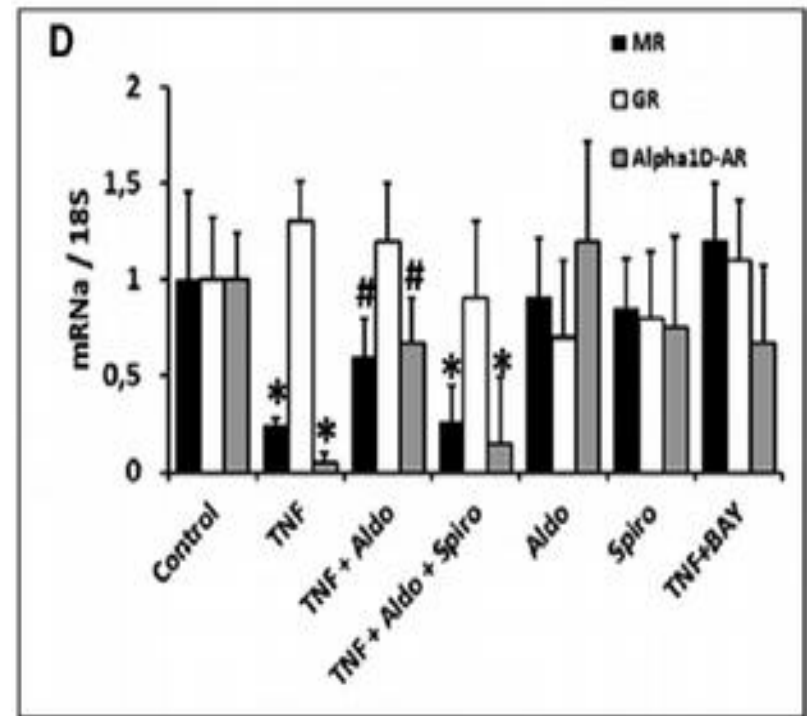
MC IMMUNE EFFECTS IN SEPSIS



MC IMMUNE EFFECTS IN SEPSIS



HUVEC experiments



Arterial smooth muscle cells

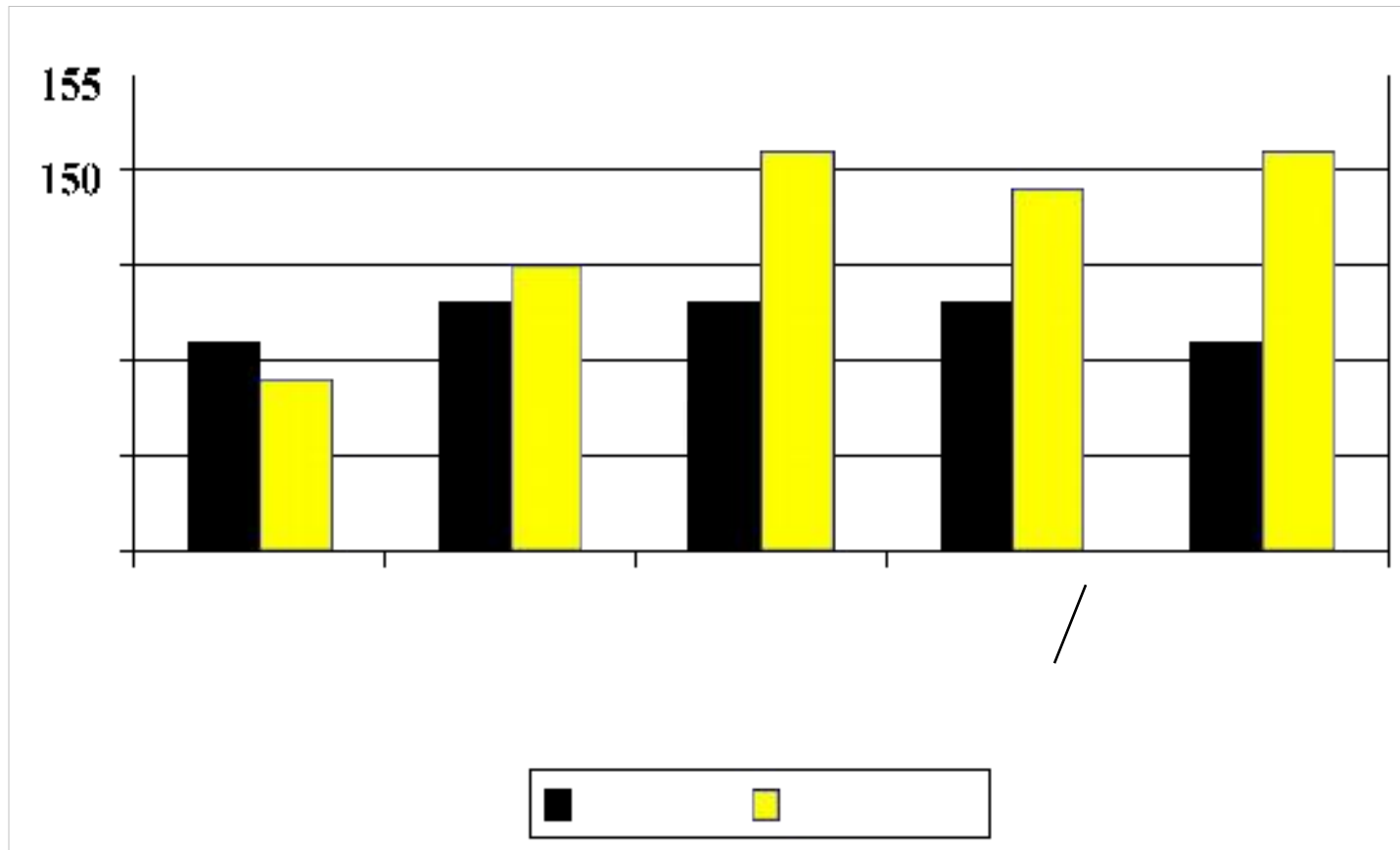


CLINICAL DATA

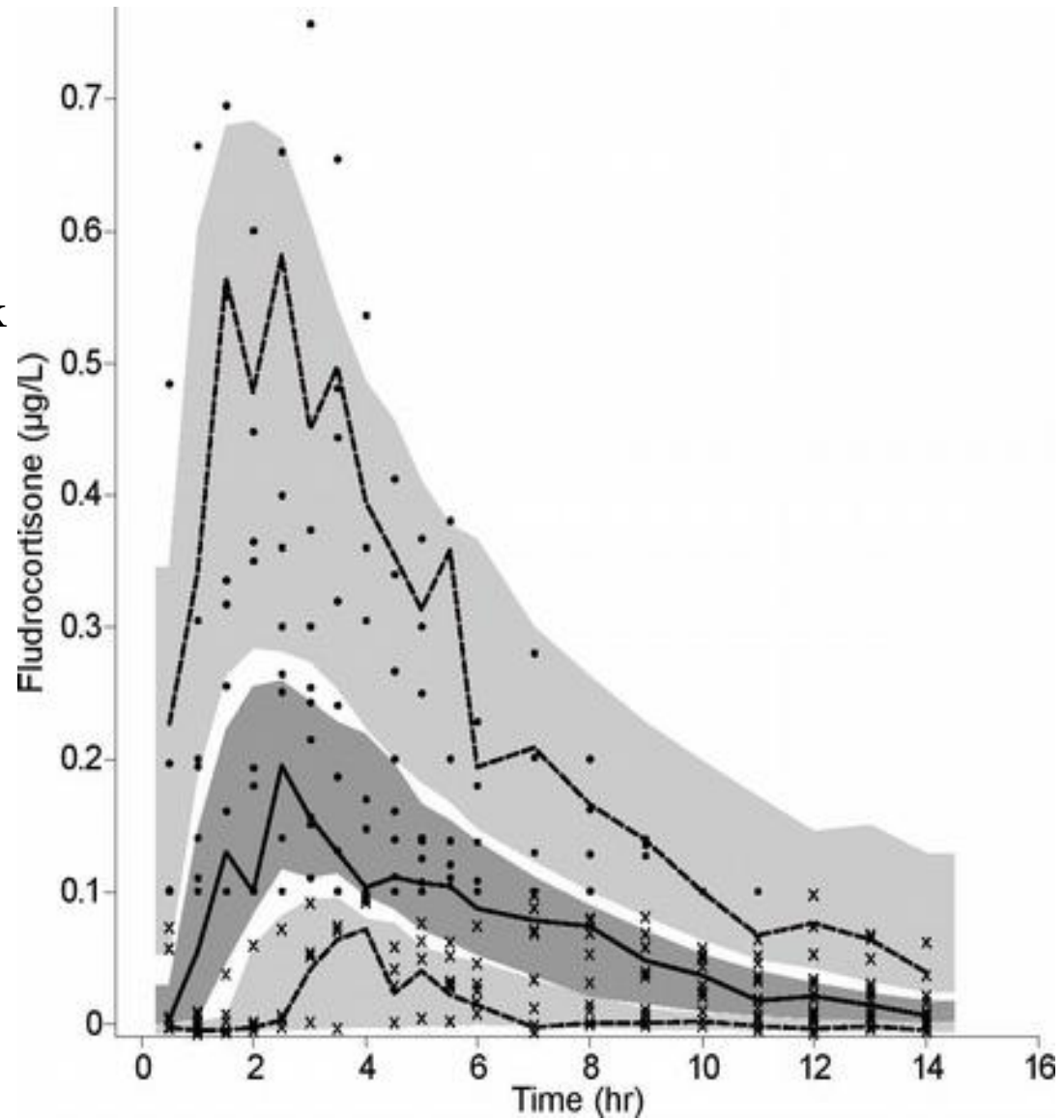
ROLE OF FLUDROCORTISONE

Mineralocorticoid effects of HC versus HC+FC

SERUM SODIUM LEVELS



N=21 adult septic shock
FC: 50µg gastric tube



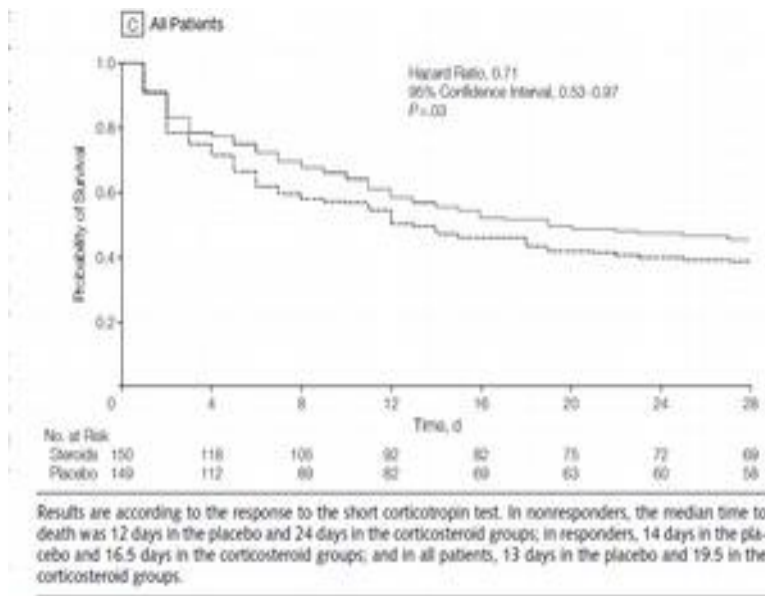
COMBINATION HYDROCORTISONE + FLUDROCORTISONE

TRIAL 1

N=300

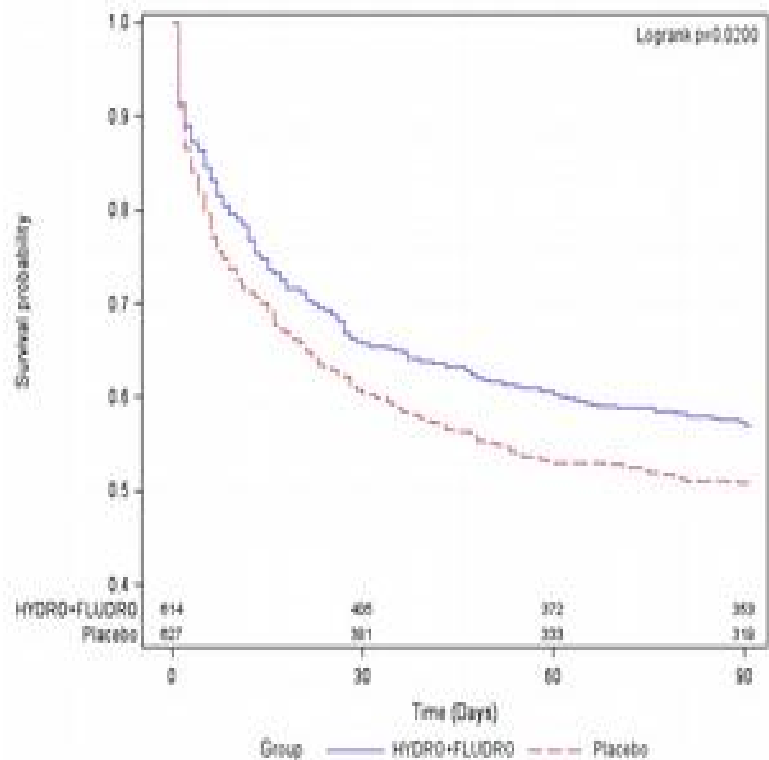
TRIAL 2

N=1241



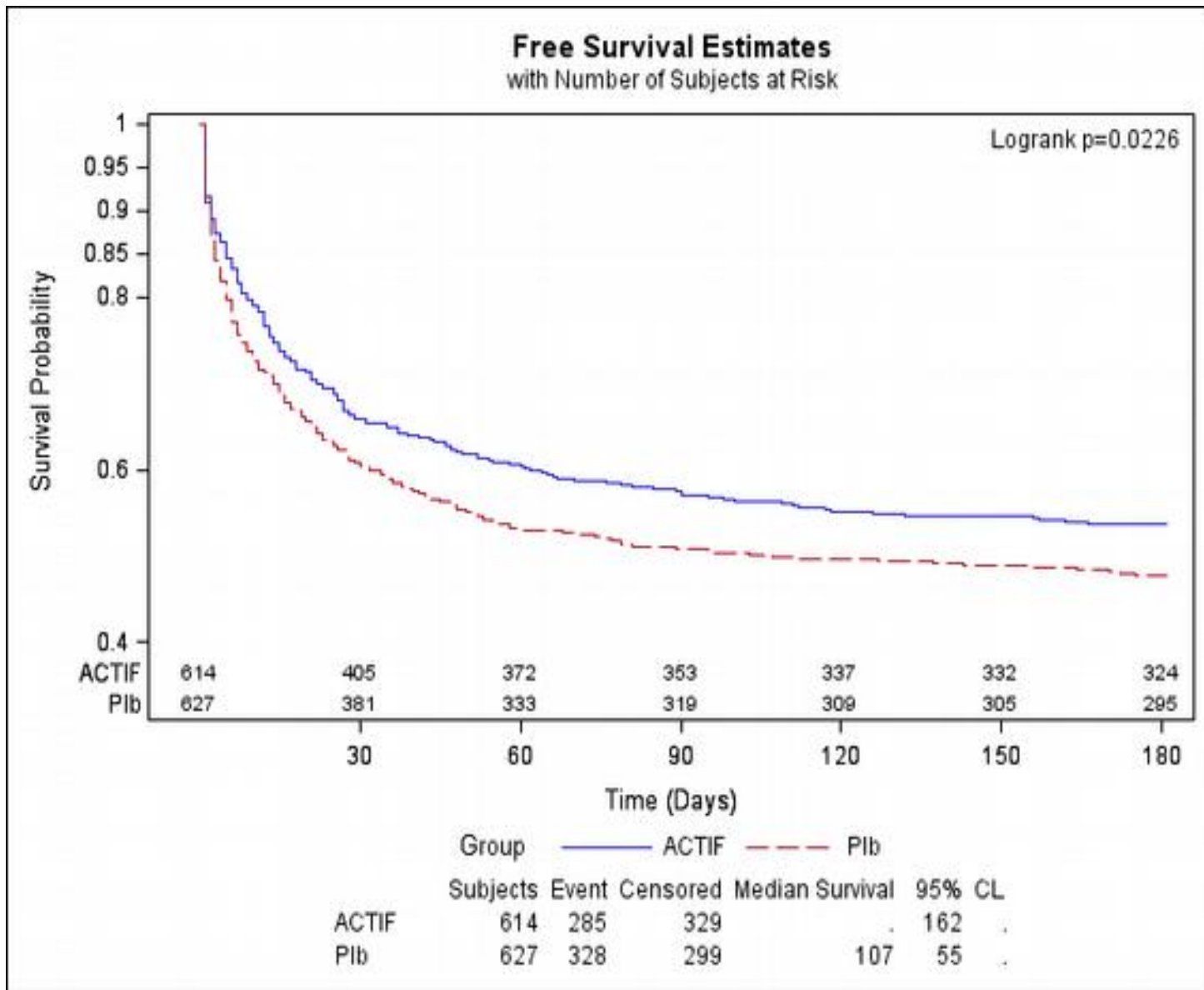
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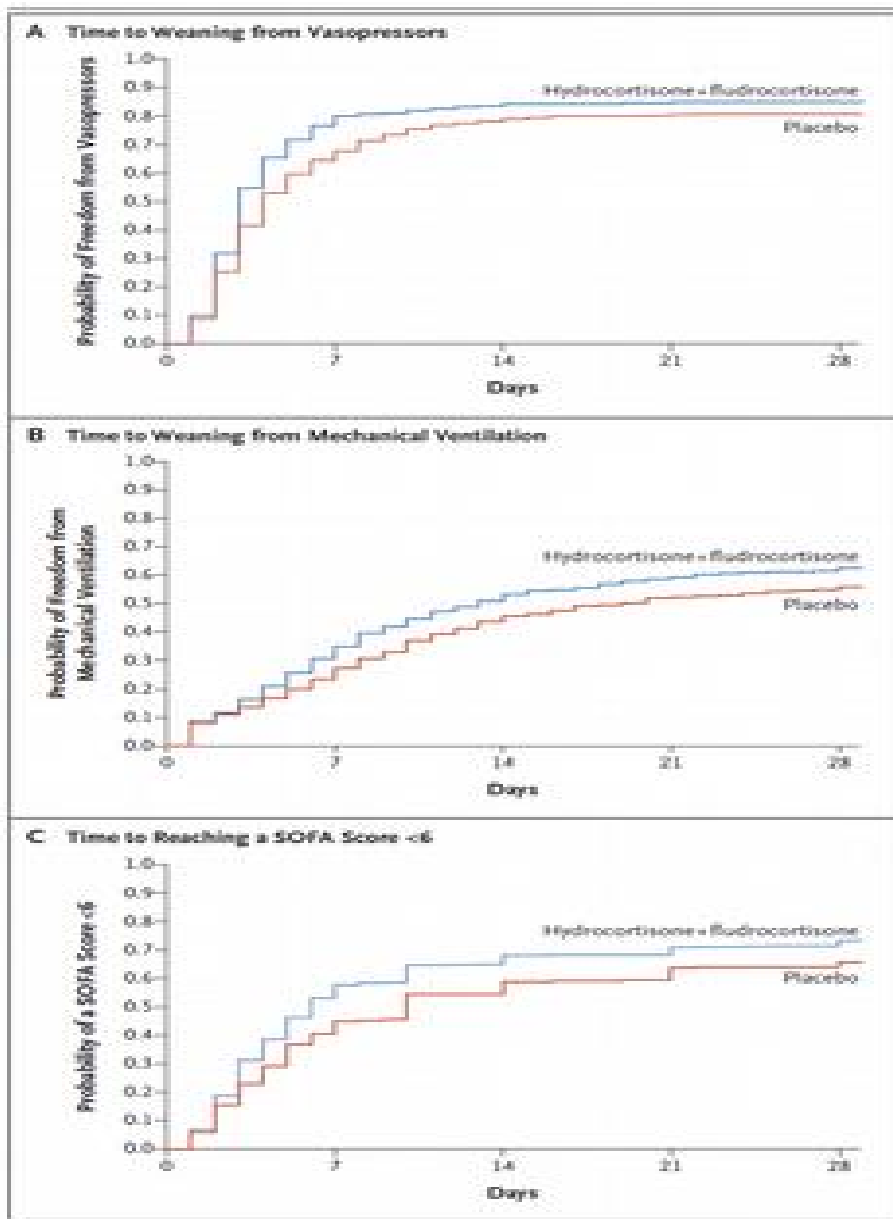
(Reprinted) JAMA, August 21, 2002—Vol 288, No. 7 867



Annane Jama 2002

Annane NEJM 2018





P<0.001

P<0.006

P<0.001



Table 3. Adverse Events.*

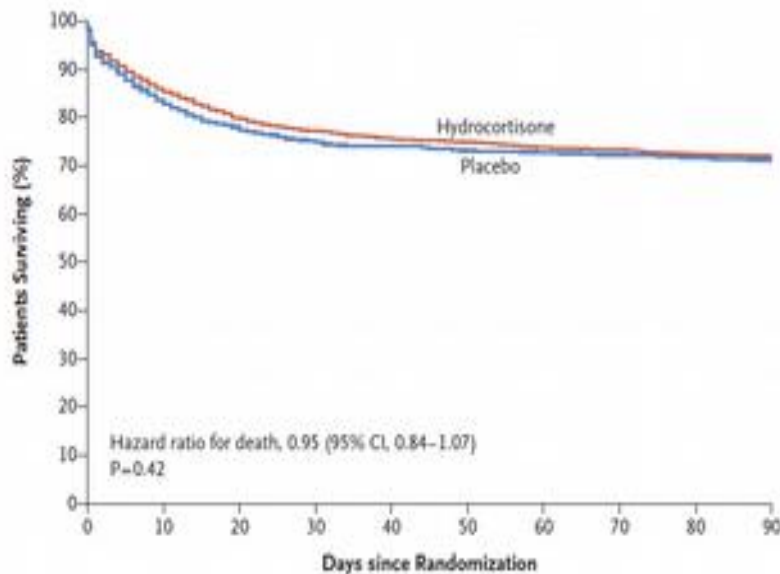
Event	Placebo (N = 627)	Hydrocortisone plus Fludrocortisone (N = 614)	Relative Risk (95% CI)†	P Value
≥1 Serious event by day 180 — no./total no. (%)	363/626 (58.0)	326/614 (53.1)	0.92 (0.83–1.01)	0.08
≥1 Serious bleeding event by day 28 — no./total no. (%)	119/626 (19.0)	127/614 (20.7)	1.09 (0.87–1.36)	0.46
Gastroduodenal bleeding — no./total no. (%)	45/626 (7.2)	39/614 (6.4)	0.88 (0.58–1.34)	0.56
≥1 Episode of superinfection by day 180 — no./total no. (%)	178/626 (28.4)	191/614 (31.1)	1.09 (0.92–1.30)	0.30
Site of superinfection — no./total no. (%)				
Lung	116/626 (18.5)	127/614 (20.7)	1.12 (0.89–1.40)	0.34
Blood	48/626 (7.7)	49/614 (8.0)	1.04 (0.71–1.53)	0.84
Catheter-related	37/626 (5.9)	40/614 (6.5)	1.10 (0.71–1.70)	0.66
Urinary tract	33/626 (5.3)	40/614 (6.5)	1.24 (0.79–1.93)	0.35
Other	57/626 (9.1)	70/614 (11.4)	1.25 (0.90–1.74)	0.18
New sepsis — no./total no. (%)	122/626 (19.5)	134/614 (21.8)	1.12 (0.90–1.39)	0.31
New septic shock — no./total no. (%)	103/626 (16.5)	109/614 (17.8)	1.08 (0.84–1.38)	0.54
Hyperglycemia				
≥1 Episode of blood glucose levels ≥150 mg/dl by day 7 — no./total no. (%)	520/626 (83.1)	547/614 (89.1)	1.07 (1.03–1.12)	0.002
No. of days with ≥1 episode of blood glucose levels ≥150 mg/dl by day 7				
Mean	3.4±2.5	4.3±2.5	—	<0.001
Median (IQR)	3 (1–6)	5 (2–6)		
Neurologic sequelae by day 28 — no./total no. (%)‡				
Last MDRS score >1	130/626 (20.8)	153/614 (24.9)	1.20 (0.98–1.47)	0.08
Last MDRS score >3	92/626 (14.7)	108/614 (17.6)	1.20 (0.93–1.54)	0.17
Last MDRS score =5	65/626 (10.4)	73/614 (11.9)	1.15 (0.84–1.57)	0.40



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*

A Survival



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

- N=3658
- HC 200 mg/d IV infusion vs placebo for 7 d or until death or d/c from ICU



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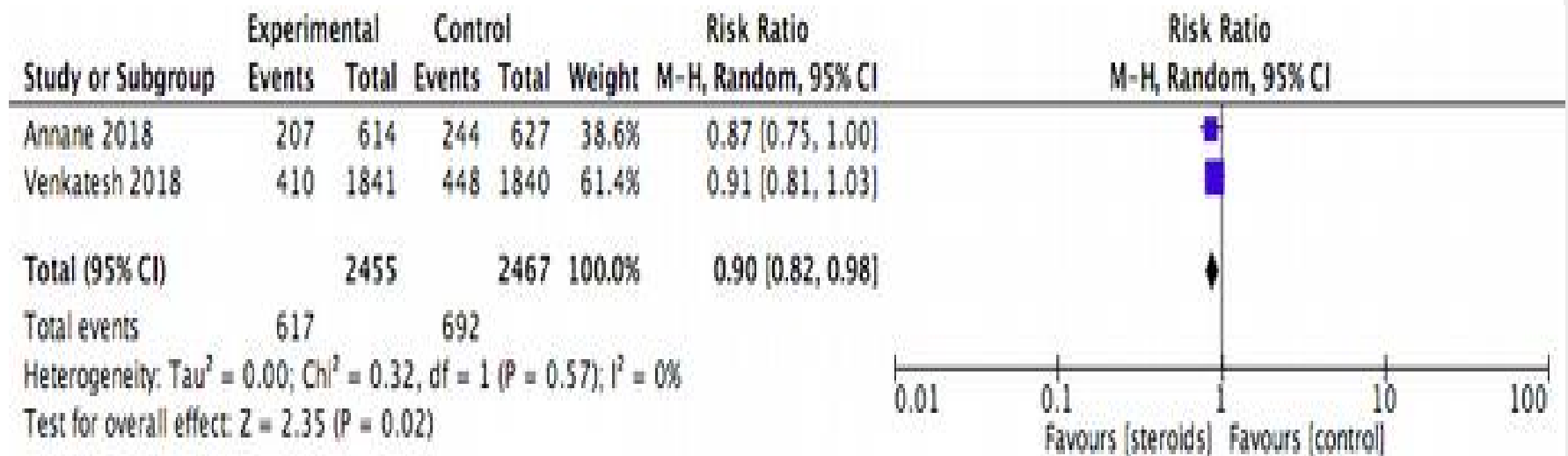
- **Hydrocortisone group:**

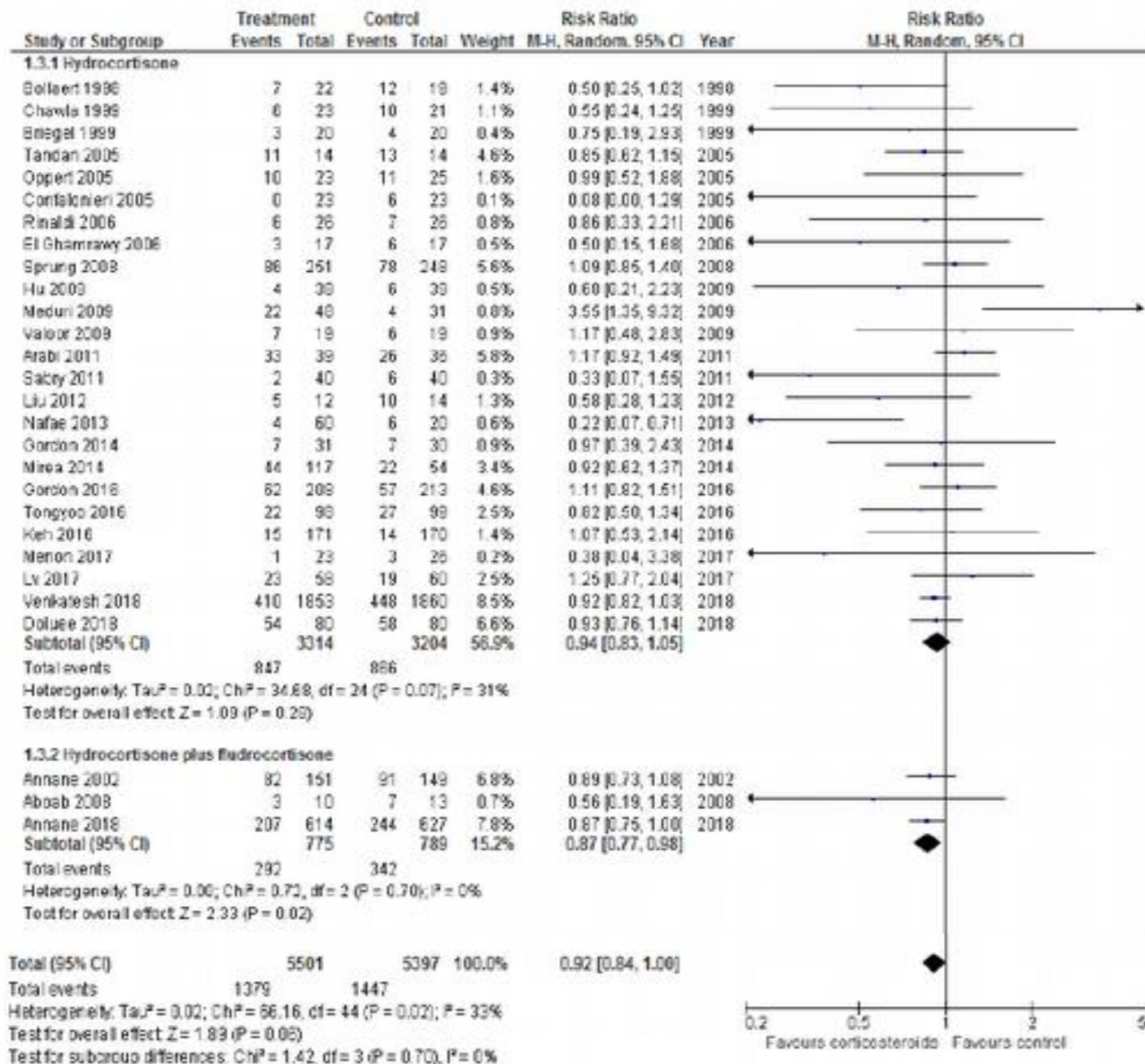
- Faster resolution of shock (median, 3d vs 4 days)
- Shorter duration of initial mechanical ventilation (median, 6 vs 7 days)
- Fewer blood transfusions
37.0% vs. 41.7%; OR, 0.82; 95% CI, 0.72 to 0.94; P = 0.004

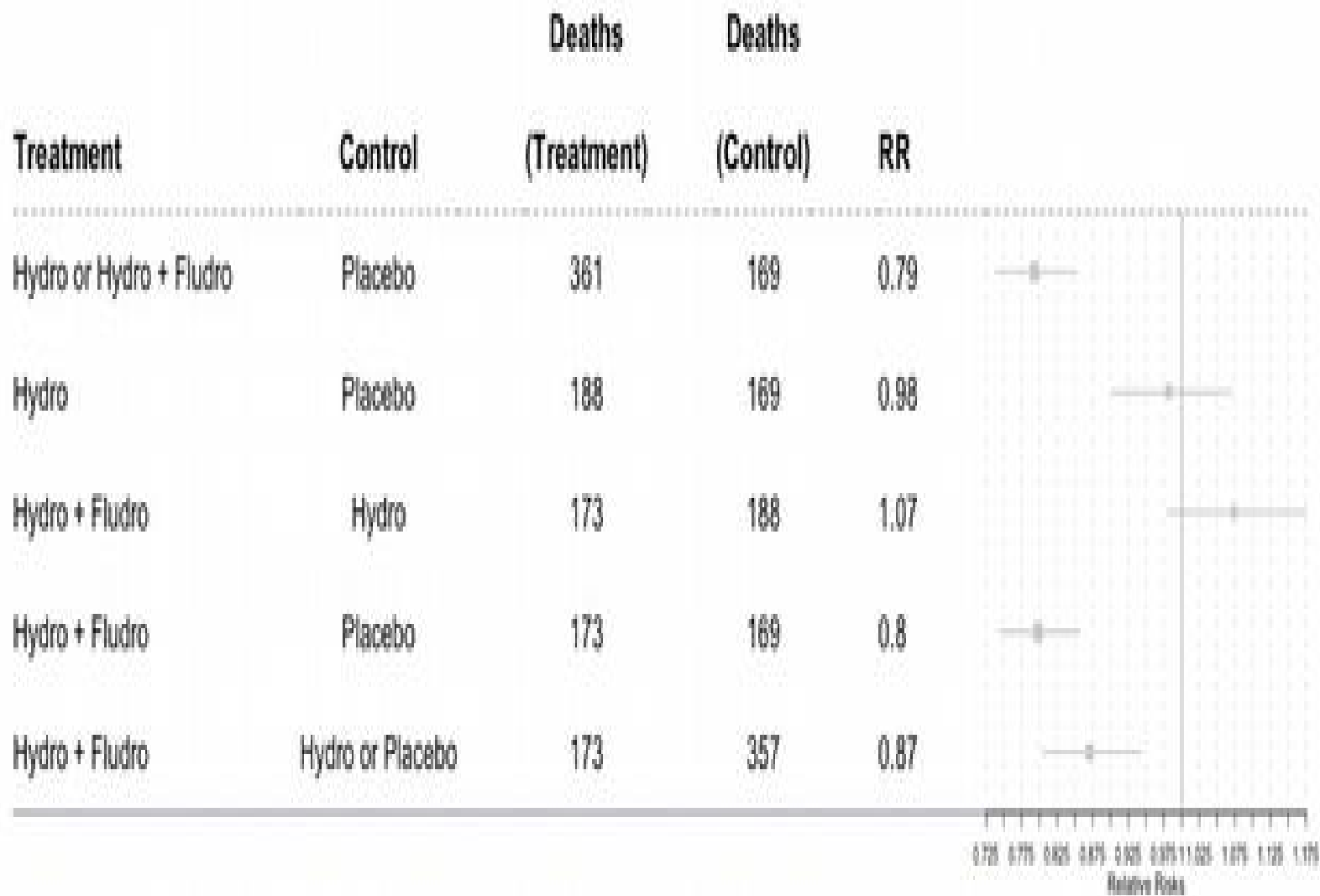
33 ADVERSE EVENTS:

- Hyperglycemia (6 HC vs 3 P)
 - Hyponatremia (3 HC vs 0 P)
 - Myopathy (3 HC vs 0 P)

COMBINED ADRENAL AND APROCCHSS







IPDMA preliminary data

IN PRATICE

- Give
 - hydrocortisone (50mg q6) +
 - fludrocortisone (50 μ g q24)
- For
 - 7 days
 - No need to taper off
- To
 - Septic shock,
 - Sepsis + ARDS,
 - Sepsis + CAP
- Not TO
 - ACTH responders, ie delta cortisol > 9 μ g/dl

