RESTE T-IL UNE PLACE POUR LES CORTICOIDES DANS LE CHOC SEPTIQUE?

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POURQUOI JE DONNE DES CS?

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)

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ICM and CCM 2017

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.

TABLE 1. Main Mechanisms of Critical Illness-Related Corticosteroid Insufficiency

General defect	Main mechanisms	Key factors
Decrease in cortisol production		
Altered adrenal synthesis of cortisol	Necrosis/hemorrhage	Acute kidney failure; hypo-coagulation; disseminated intravascular coagulation; cardiovascular collapse; tyrosine kinase inhibitors
	Decreased availability of esterified cholesterol	Depletion in adrenal storage regulated by annexin A1–formyl peptide receptors Down regulated scavenger receptor-B1
	Inhibition of steroidogenesis	Immune cells/Toll-like receptors/cytokines
		Drugs (e.g., sedatives, corticosteroids)
		ACTH-like molecules (e.g., corticostatins)
Altered synthesis of CRH/ACTH	Necrosis/hemorrhage	Cardiovascular collapse; disseminated intravascular coagulation; treatment with vasopressor agents
	Inhibition of ACTH synthesis	Glial cells/nitric oxide mediated neuronal apoptosis
		Increased negative feedback from circulating cortisol following up regulation of ACTH-independent mechanisms of cortisol synthesis
		Drugs (e.g., sedatives, anti-infective, psychoactive agents)
		Inappropriate cessation of glucocorticoid treatment
Alteration of cortisol metabolism	Decreased cortisol transport	Down regulation of liver synthesis of cortisol-binding globulins and albumin
	Reduced cortisol breakdown	Decreased expression and activity of the glucocorticoid-inactivating 5-reductase enzymes in the liver with putative role of bile acids; Decreased expression and activity of the hydroxysteroid dehydrogenase in the kidney
Target tissue resistance to cortisol	Inadequate glucocorticoid receptor alpha (GR-α) activity	Multifactorial etiology including reduced GR-α density and transcription and excessive NF-kappa B activation

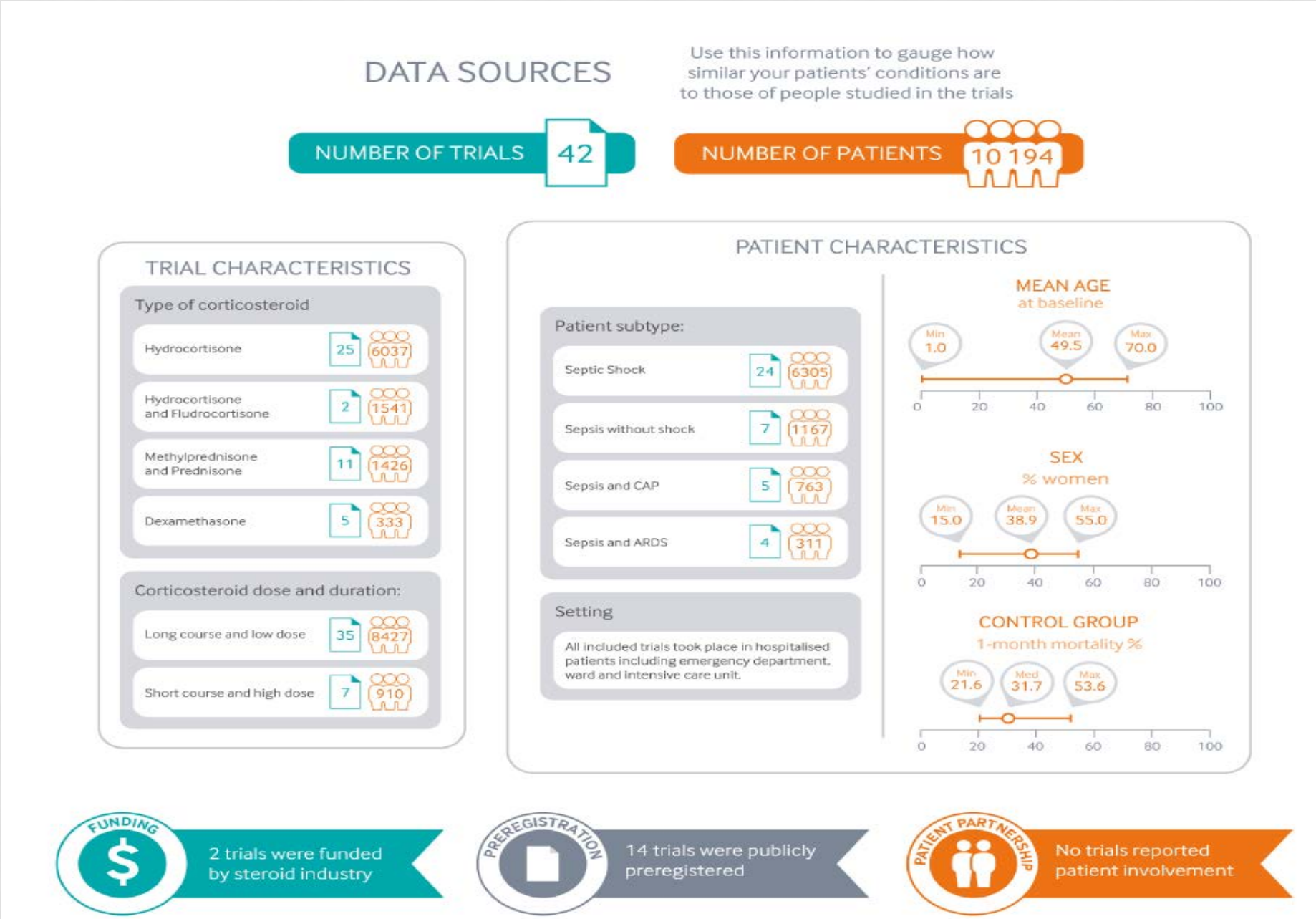
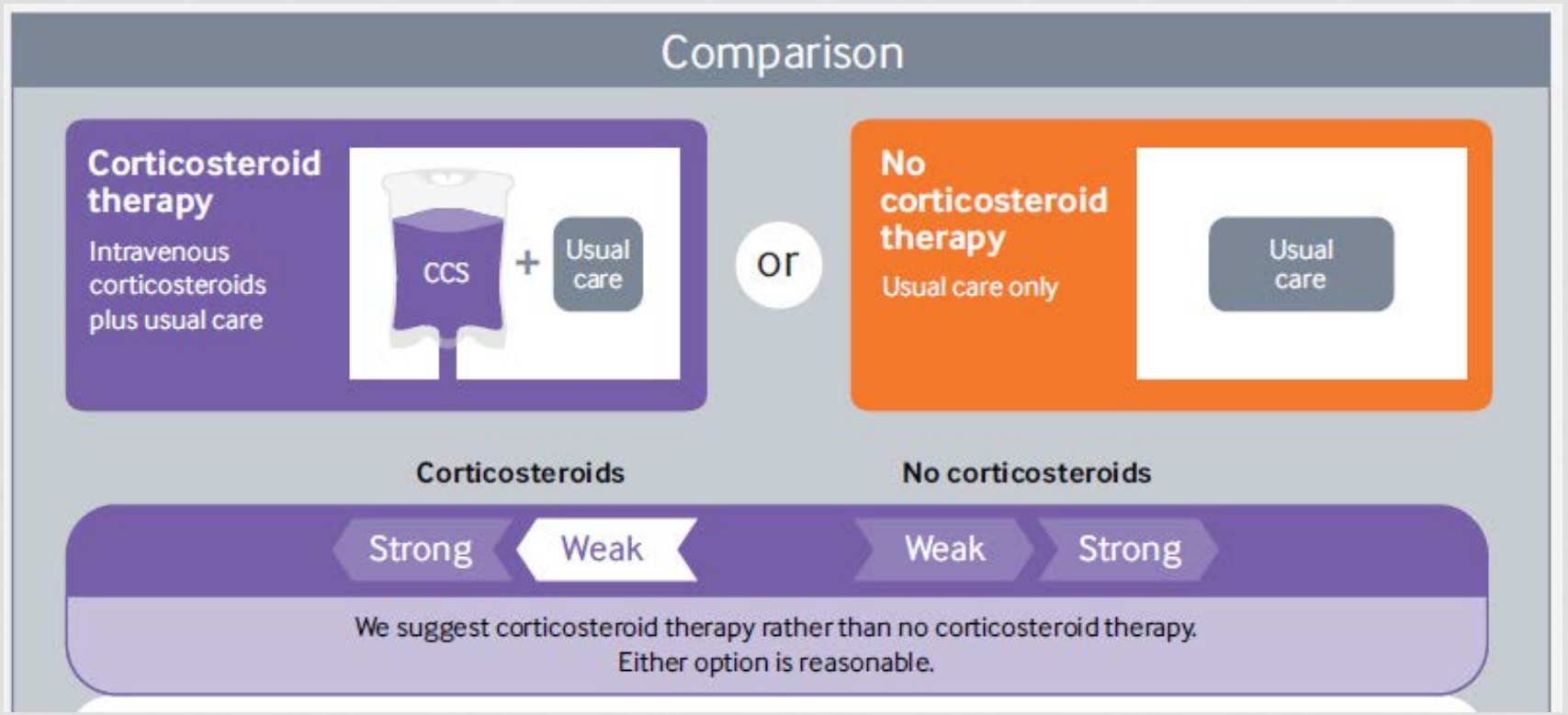
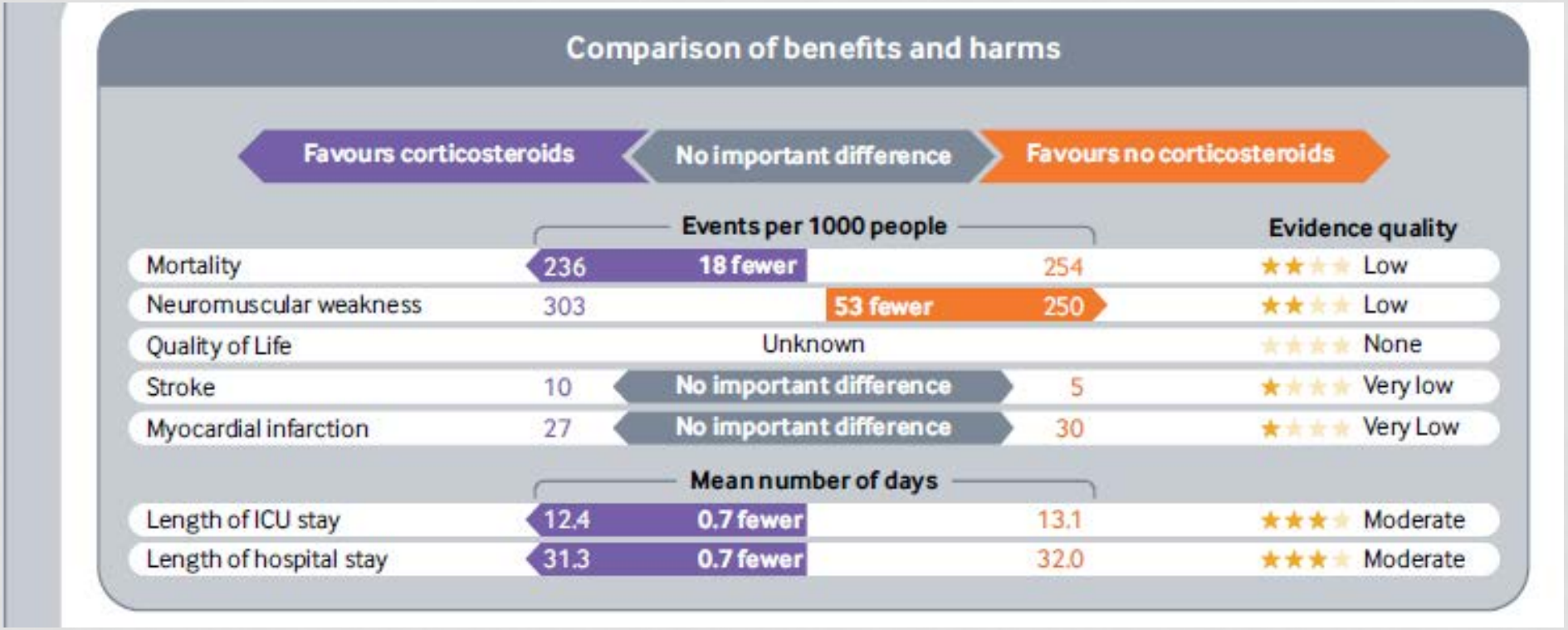


Fig 2| Characteristics of patients and trials included in systematic review of the use of corticosteroids for treating sepsis[3]
CAP=community acquired pneumonia. ARDS=acute respiratory distress syndrome.

Lamontagne BMJ 2018



Lamontagne BMJ 2018



Lamontagne BMJ 2018

COMMENT J'UTILE LES CS?

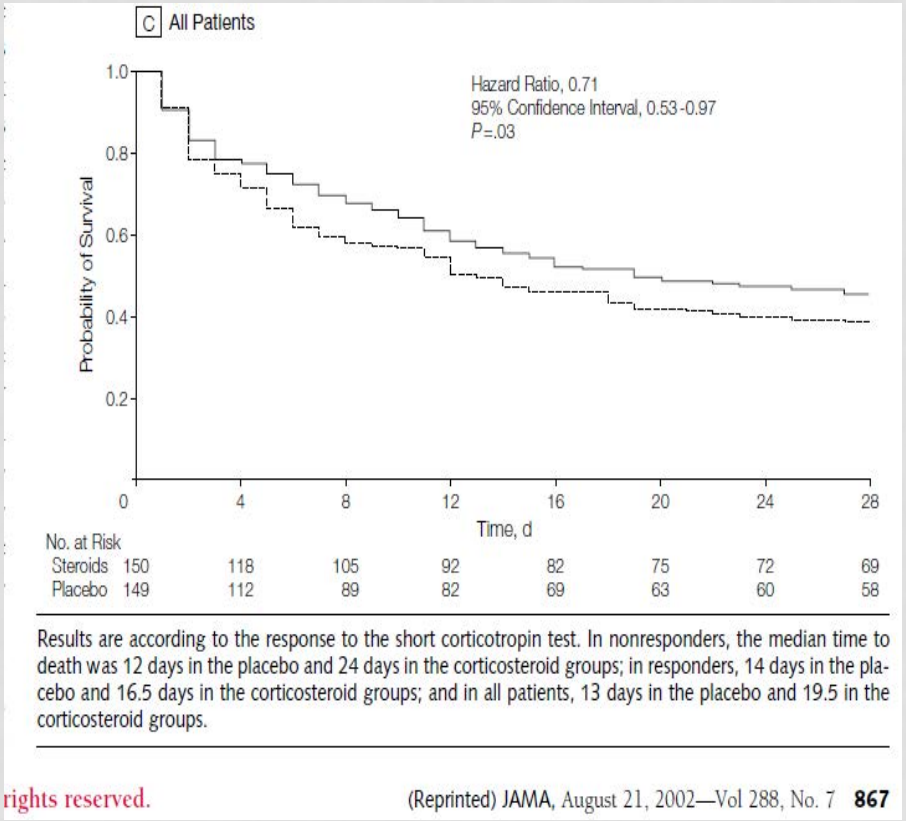
ALL CORTICOSTEROIDS ARE NOT EQUIVALENT

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	0
Dexamethasone	25	0	20
Fludrocortisone	10	125	?

Annane & Heming, Scientific American – Crit Care of the Surg Patient 2017

COMBINATION HYDROCORTISONE + FLUDROCORTISONE

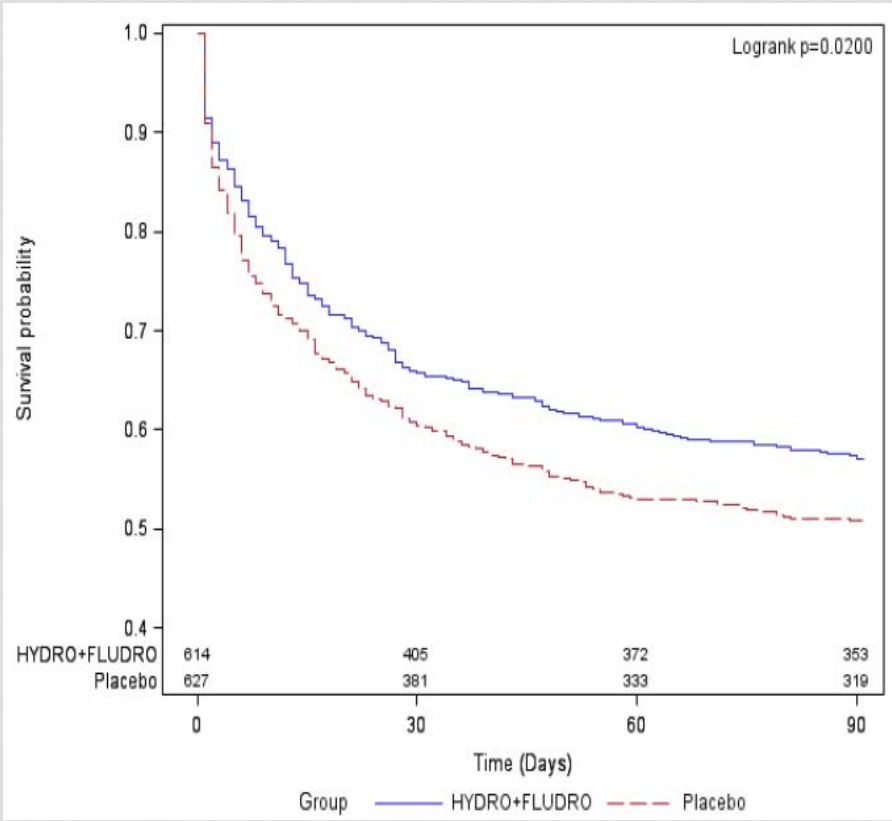
TRIAL 1
N=300



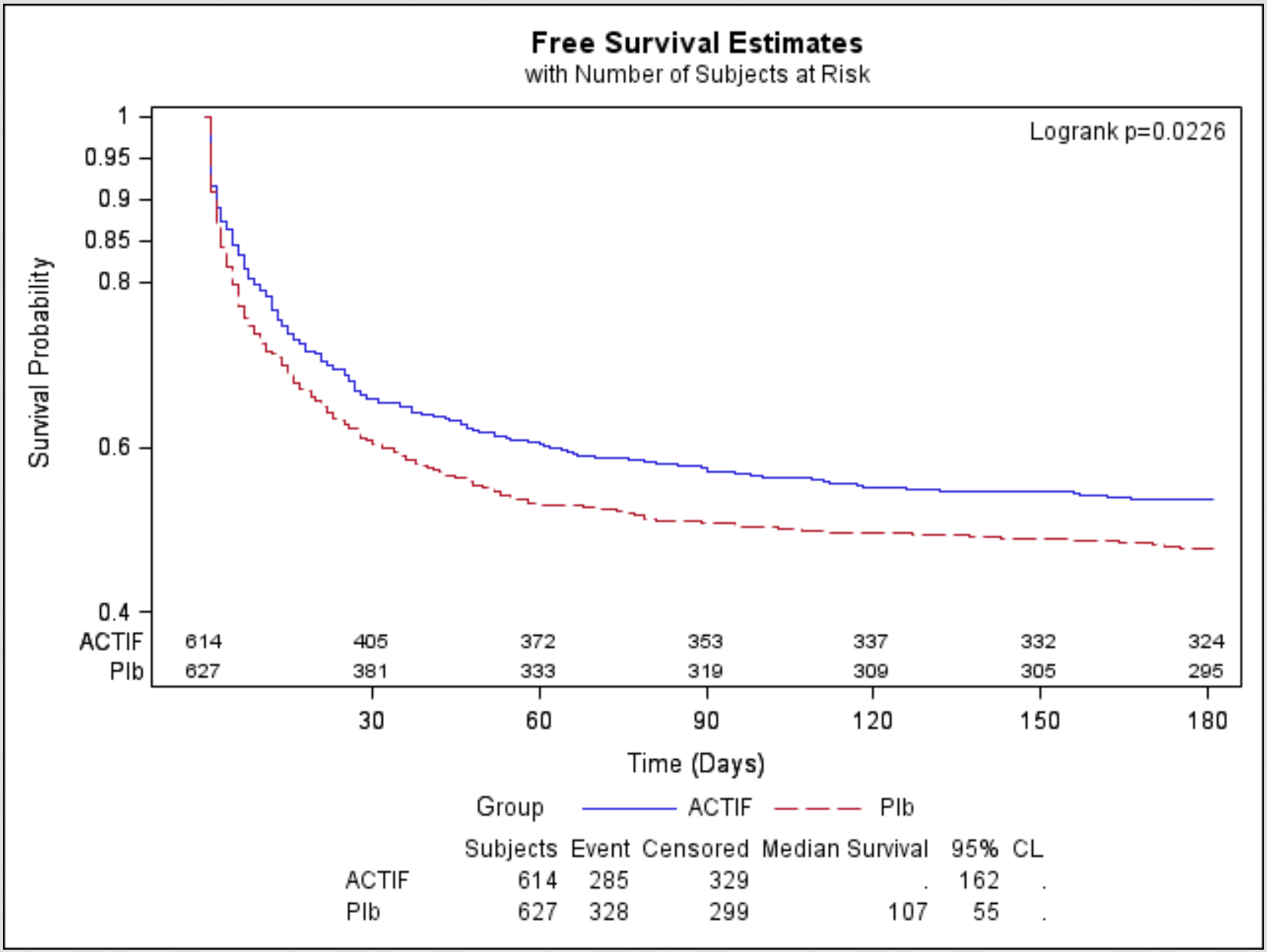
Results are according to the response to the short corticotropin test. In nonresponders, the median time to death was 12 days in the placebo and 24 days in the corticosteroid groups; in responders, 14 days in the placebo and 16.5 days in the corticosteroid groups; and in all patients, 13 days in the placebo and 19.5 in the corticosteroid groups.

Annane Jama 2002

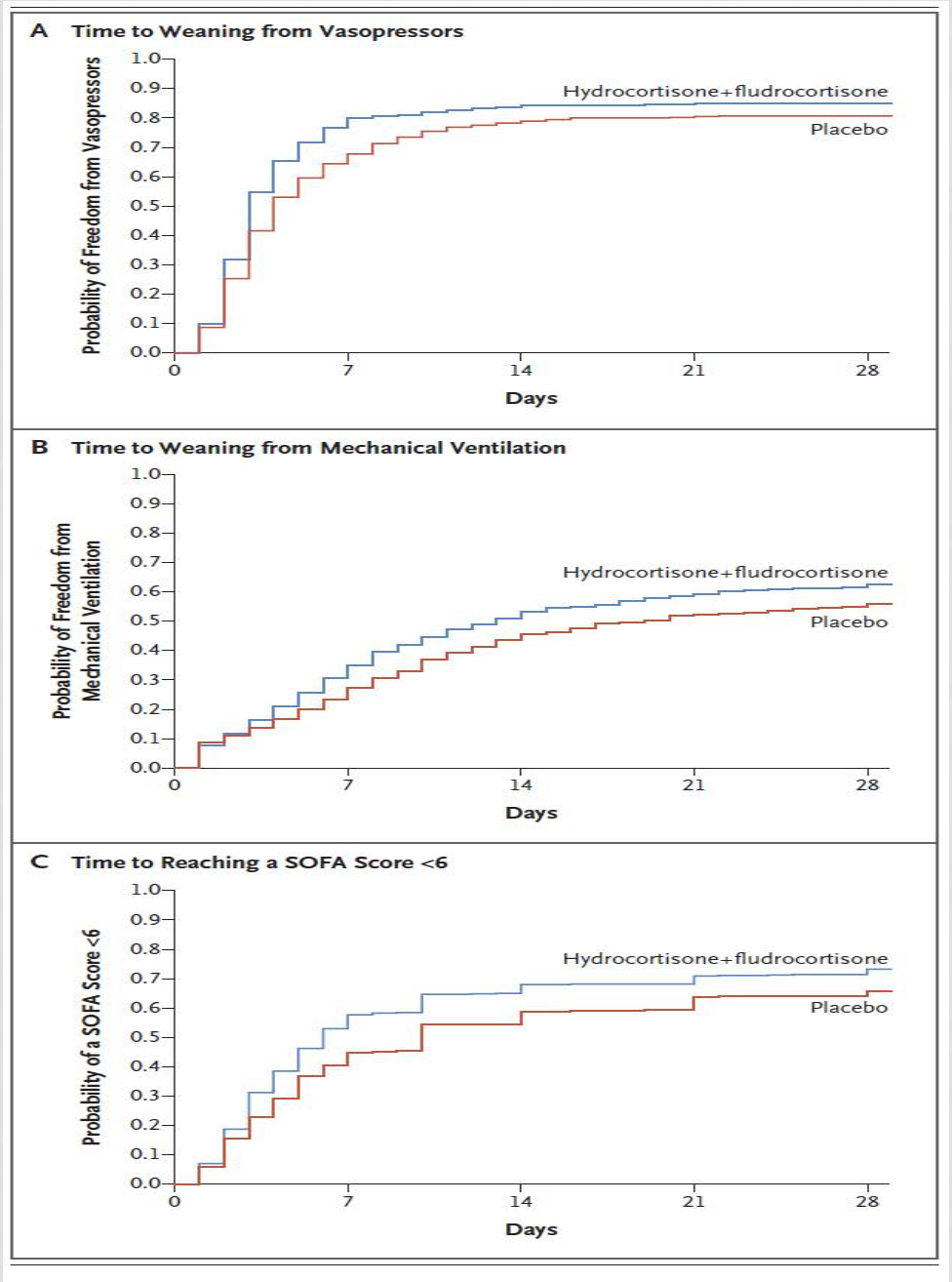
TRIAL 2
N=1241



Annane NEJM 2018



Annane NEJM 2018



P<0.001

P<0.006

P<0.001

Annane et al NEJM 2018

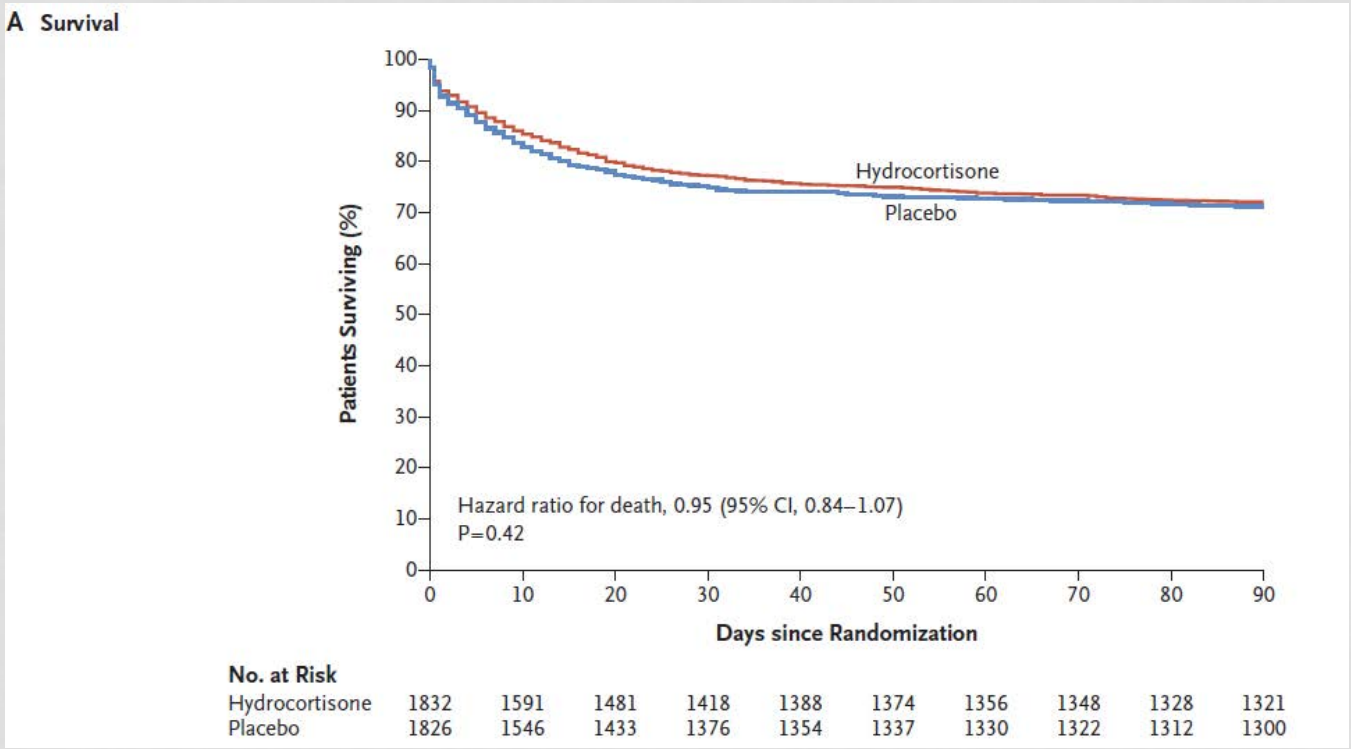
Table 3. Adverse Events.*

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

Annane et al NEJM 2018

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*



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

NEJM 2018

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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)
- Hypernatremia (3 HC vs 0 P)
- Myopathy (3 HC vs 0 P)

NEJM 2018

DIFFERENCES BETWEEN ADRENAL AND APROCCHSS

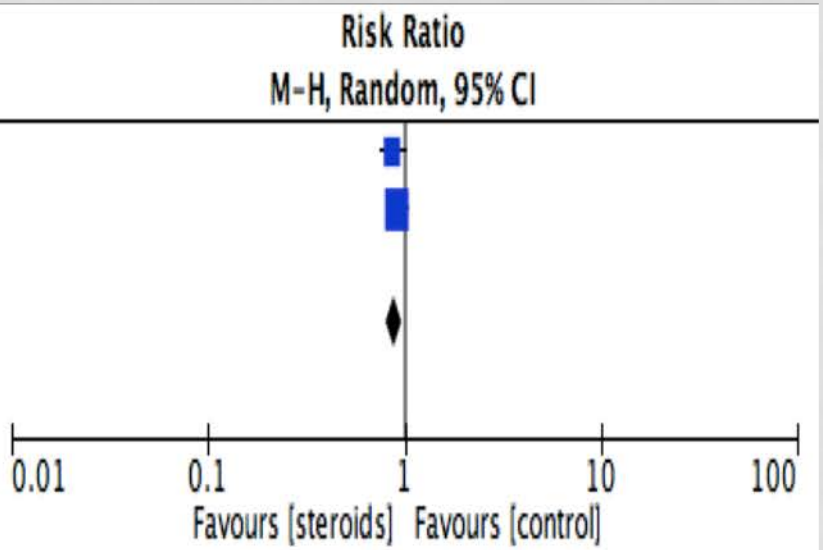
- Fludrocortisone added to HC in APROCCHSS
- HC given as 50 mg IV bolus q 6h + PO fludro 50 mcg tablet once daily x 7 days in APROCCHSS vs.
  HC continuous infusion 200 mg/day x 7 days or until death or ICU discharge in ADRENAL
- ADRENAL: higher rate of surgical admissions, lower rate of RRT, lower rates of lung infection and UTI and higher rate of abdominal infections
- APROCCHSS: high SOFA and SAPS II values (sicker population)

COMBINED ADRENAL AND APROCCHSS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2018	207	614	244	627	38.6%	0.87 [0.75, 1.00]
Venkatesh 2018	410	1841	448	1840	61.4%	0.91 [0.81, 1.03]
Total (95% CI)		**2455**		**2467**	**100.0%**	**0.90 [0.82, 0.98]**
Total events	617		692			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0\%$

Test for overall effect: Z = 2.35 (P = 0.02)



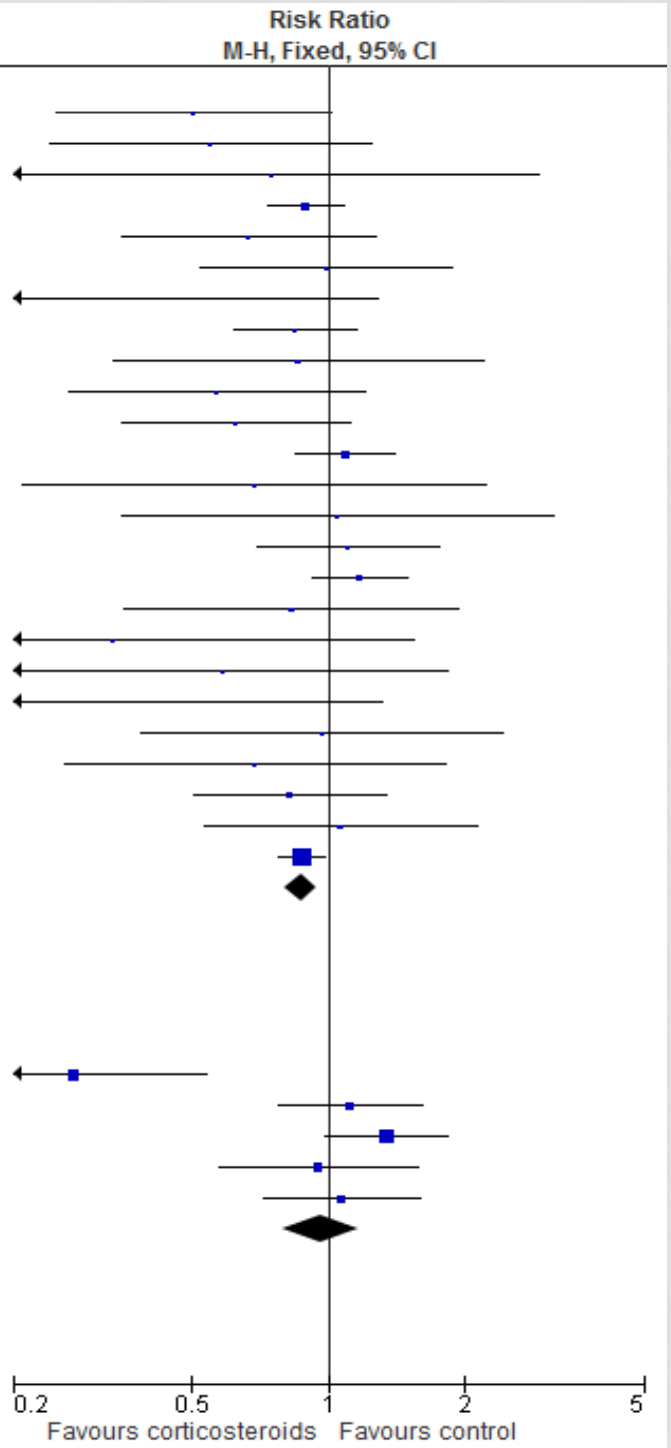
Rochwerg CCM 2018

A QUELLE DOSE & DUREE?

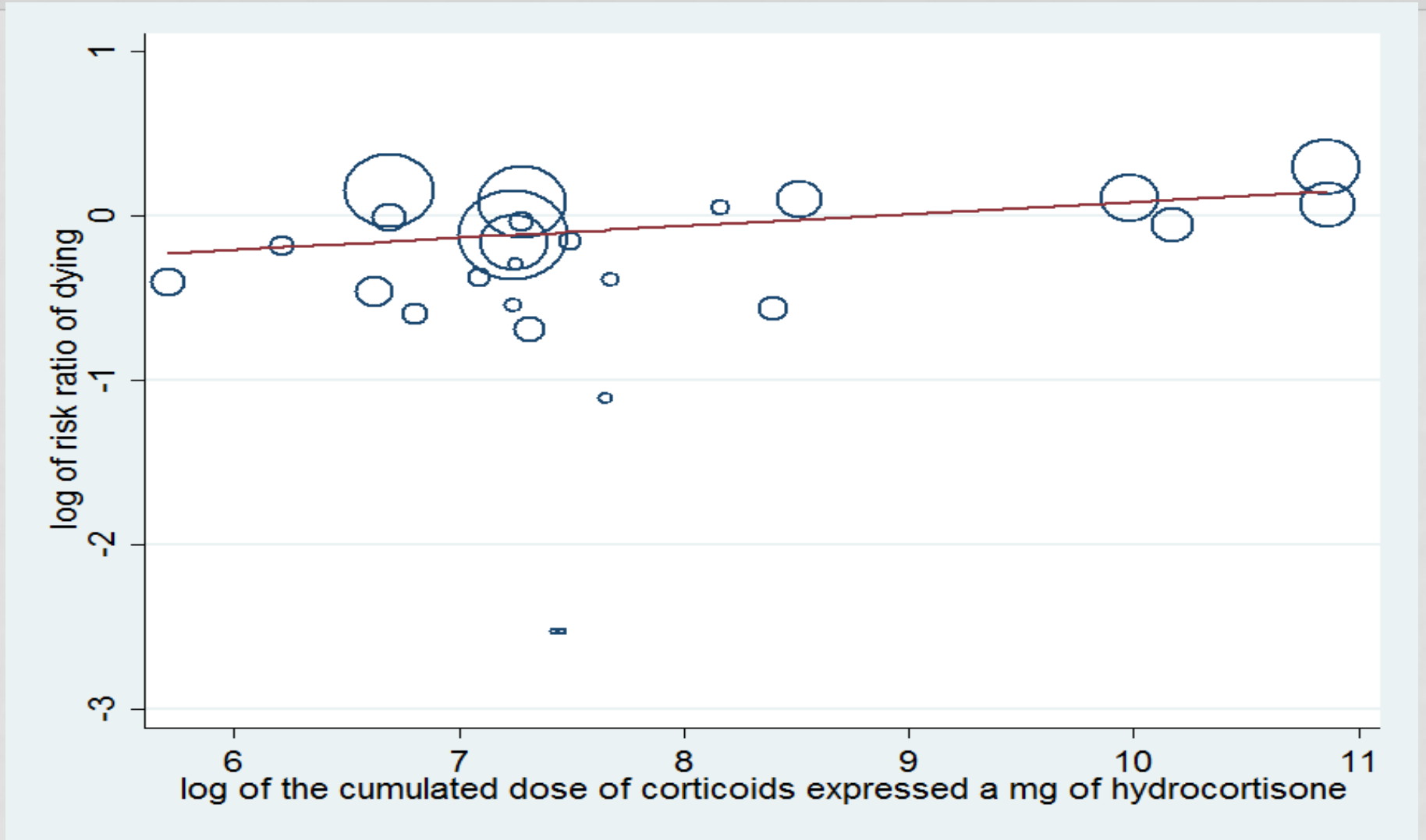
>400 mg/day HC equivalent <24h

<400mg/day HC equivalent >72 h

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.4.1 Long course of low-dose corticosteroids							
Bollaert 1998	7	22	12	19	1.8%	0.50 [0.25, 1.02]	1998
Chawla 1999	6	23	10	21	1.5%	0.55 [0.24, 1.25]	1999
Briegel 1999	3	20	4	20	0.6%	0.75 [0.19, 2.93]	1999
Annane 2002	82	151	91	149	12.9%	0.89 [0.73, 1.08]	2002
Yildiz 2002	8	20	12	20	1.7%	0.67 [0.35, 1.27]	2002
Oppert 2005	10	23	11	25	1.5%	0.99 [0.52, 1.88]	2005
Confalonieri 2005	0	23	6	23	0.9%	0.08 [0.00, 1.29]	2005
Tandan 2005	11	14	13	14	1.8%	0.85 [0.62, 1.15]	2005
Rinaldi 2006	6	26	7	26	1.0%	0.86 [0.33, 2.21]	2006
Meduri 2007	10	42	8	19	1.5%	0.57 [0.27, 1.20]	2007
Cicarelli 2007	7	14	12	15	1.6%	0.63 [0.35, 1.12]	2007
Sprung 2008	86	251	78	248	11.0%	1.09 [0.85, 1.40]	2008
Hu 2009	4	38	6	39	0.8%	0.68 [0.21, 2.23]	2009
Snijders 2010	6	104	6	109	0.8%	1.05 [0.35, 3.15]	2010
Yildiz 2011	16	27	15	28	2.1%	1.11 [0.69, 1.76]	2011
Arabi 2011	33	39	26	36	3.8%	1.17 [0.92, 1.49]	2011
Meijvis 2011	9	151	11	153	1.5%	0.83 [0.35, 1.94]	2011
Sabry 2011	2	40	6	40	0.8%	0.33 [0.07, 1.55]	2011
Liu 2012	3	12	6	14	0.8%	0.58 [0.18, 1.85]	2012
Rezk 2013	0	18	3	9	0.6%	0.08 [0.00, 1.32]	2013
Gordon 2014	7	31	7	30	1.0%	0.97 [0.39, 2.43]	2014
Torres 2015	6	59	9	61	1.2%	0.69 [0.26, 1.82]	2015
Tongyoo 2016	22	98	27	99	3.8%	0.82 [0.50, 1.34]	2016
Keh 2016	15	171	14	170	2.0%	1.07 [0.53, 2.14]	2016
Annane 2017	264	614	308	627	42.8%	0.88 [0.78, 0.99]	2017
Subtotal (95% CI)		**2031**		**2014**	**100.0%**	**0.87 [0.81, 0.95]**	
Total events	623		708				
Heterogeneity: Chi² = 25.25, df = 24 (P = 0.39); I² = 5%							
Test for overall effect: Z = 3.29 (P = 0.001)							
1.4.2 Short course of high-dose corticosteroids							
Schumer 1976	9	86	33	86	23.3%	0.27 [0.14, 0.53]	1976
Sprung 1984	33	43	11	16	11.3%	1.12 [0.77, 1.61]	1984
Bone 1987	65	191	48	190	34.0%	1.35 [0.98, 1.84]	1987
VASSCSG 1987	23	112	24	111	17.0%	0.95 [0.57, 1.58]	1987
Luce 1988	22	38	20	37	14.3%	1.07 [0.72, 1.60]	1988
Subtotal (95% CI)		**470**		**440**	**100.0%**	**0.96 [0.80, 1.16]**	
Total events	152		136				
Heterogeneity: Chi² = 18.73, df = 4 (P = 0.0009); I² = 79%							
Test for overall effect: Z = 0.39 (P = 0.70)							
Test for subgroup differences: Chi² = 0.87, df = 1 (P = 0.35), I² = 0%							

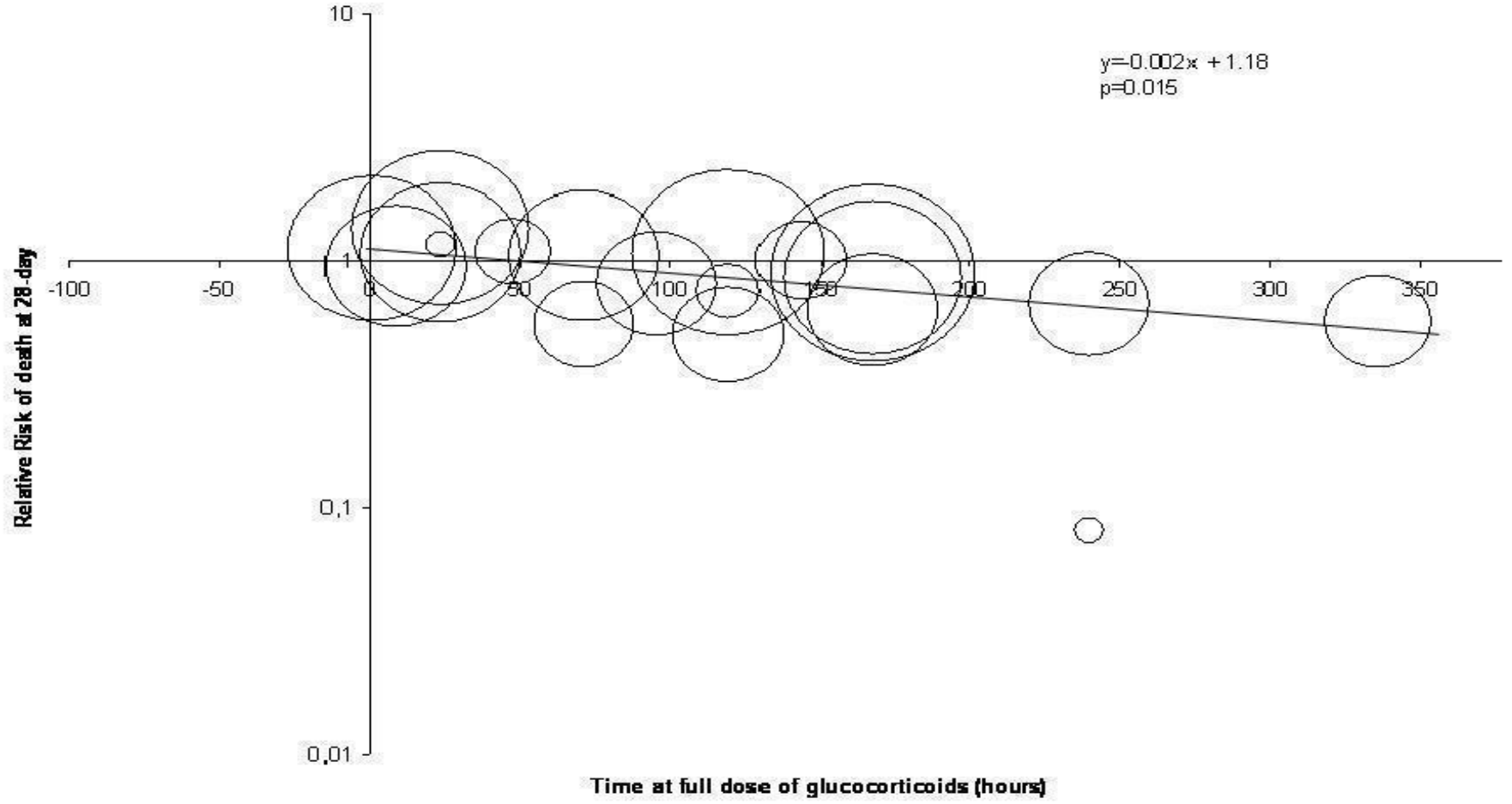


CORTICOSTEROIDS DOSE THE LOWER THE BETTER



Annane CDSR 2015

CORTICOSTEROIDS DURATION
THE LONGER THE BETTER



Annane CDSR 2015

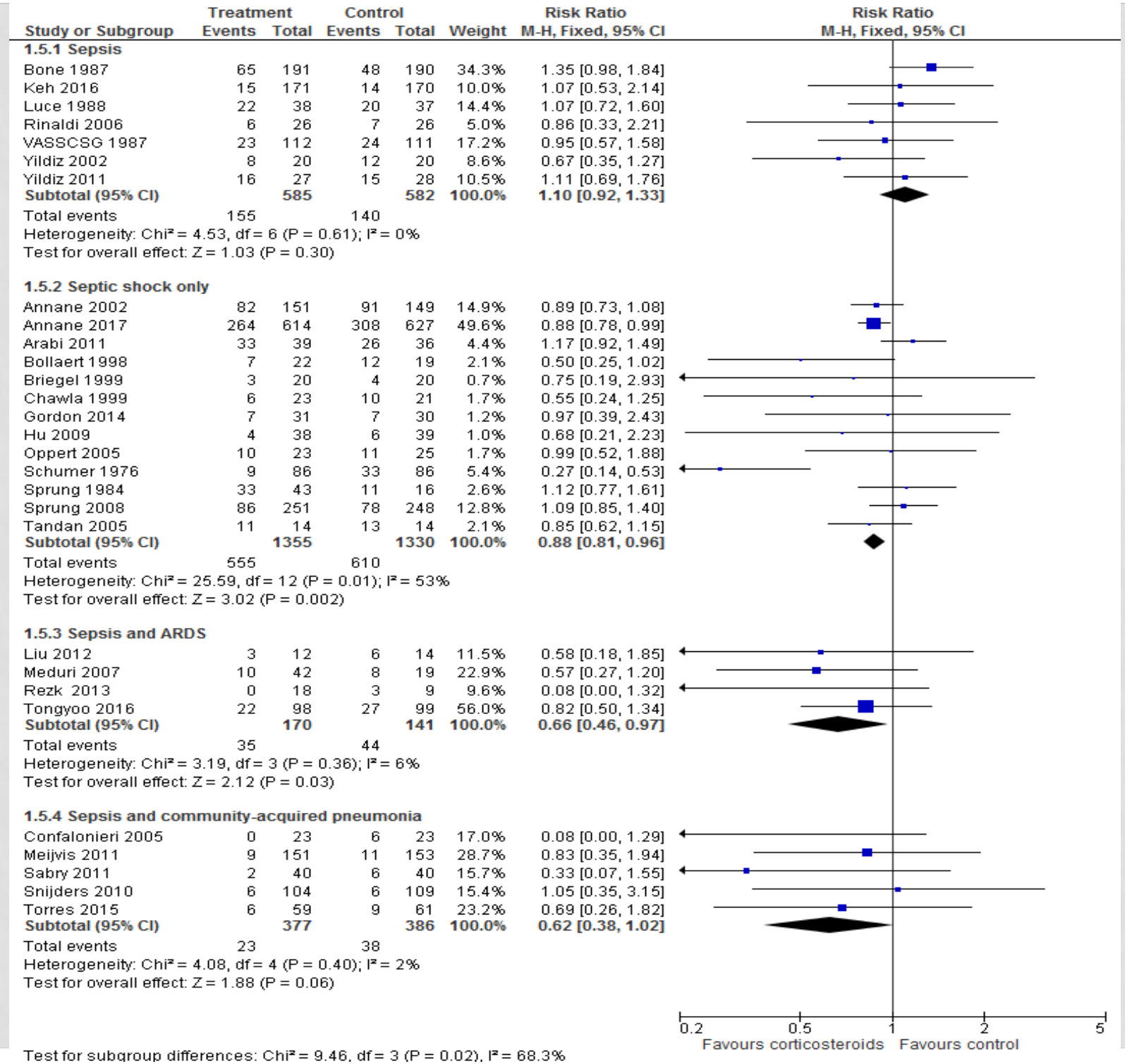
A QUI J'EN DONNE?

Sepsis

Septic shock

ARDS

CAP



Test for subgroup differences: Chi² = 9.46, df = 3 (P = 0.02), I² = 68.3%

DIAGNOSTIC TEST

ADRENAL STATUS

Interaction between
treatment effects and
ACTH test status
Simon and Gail p<0.001

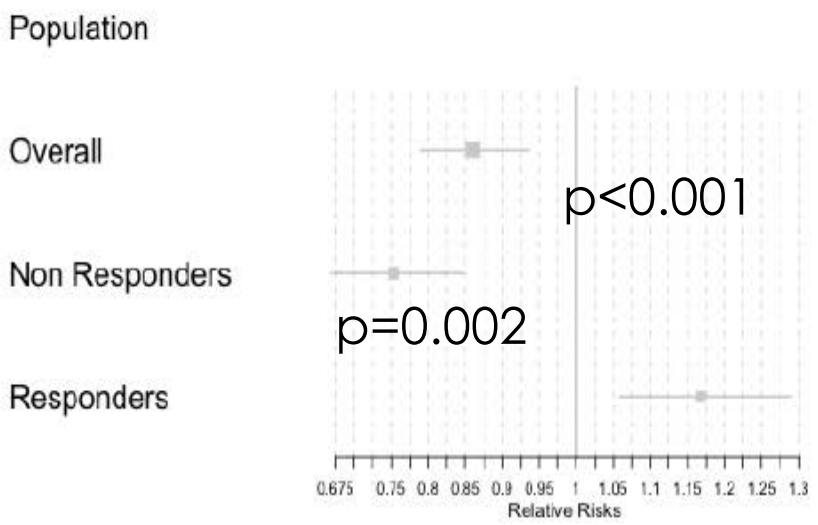
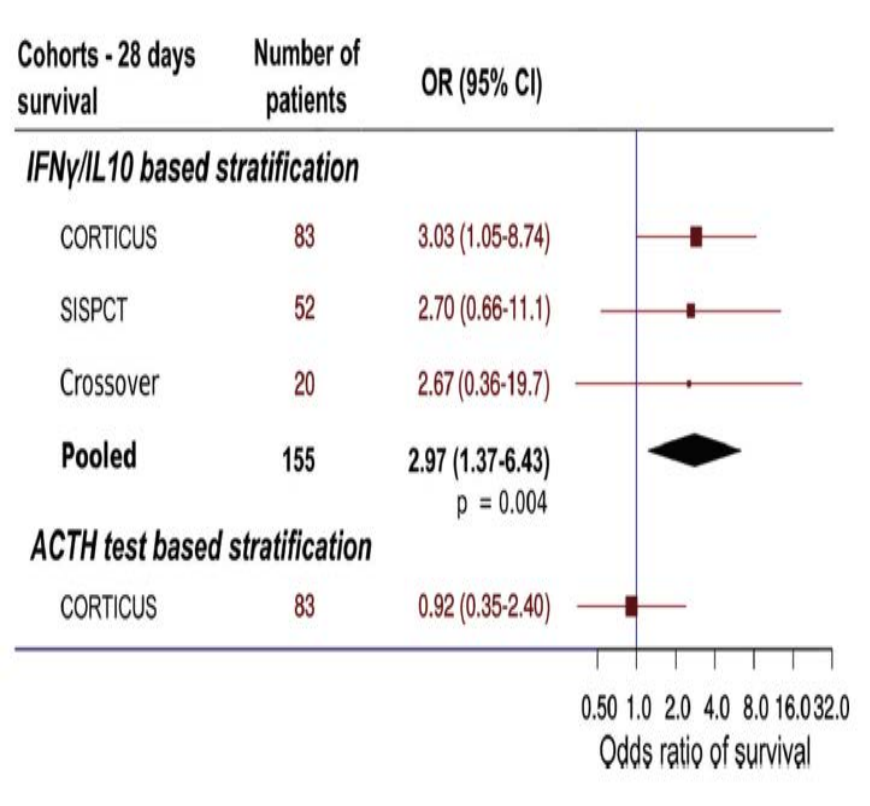


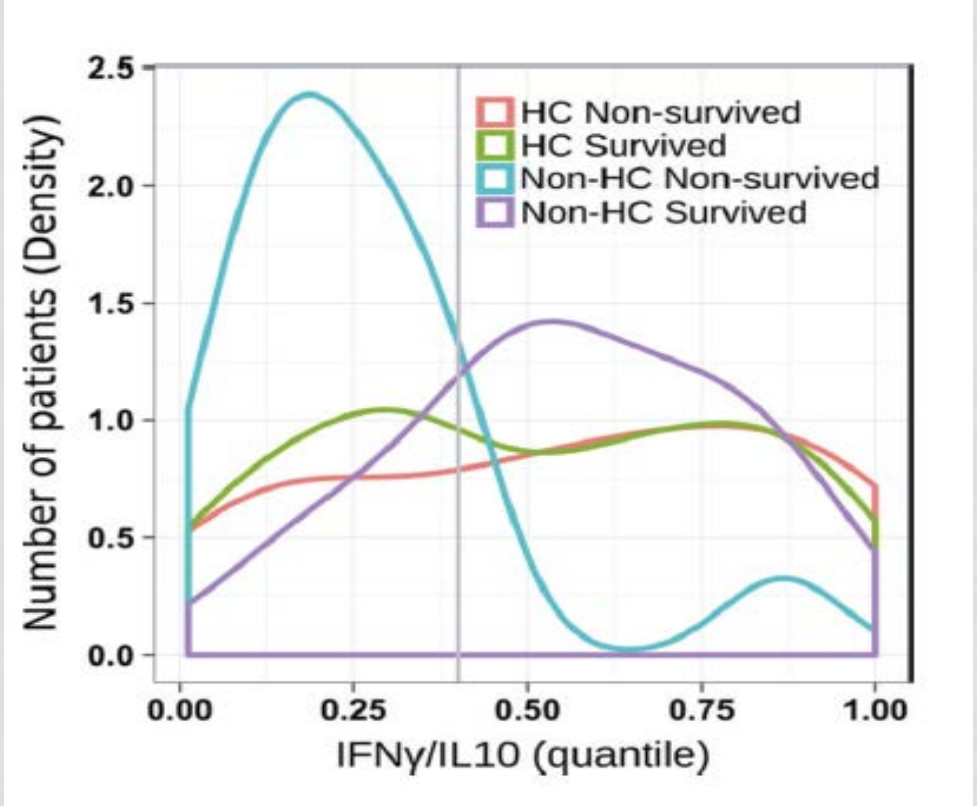
Figure 3: Treatment Effect by Response to the Corticotropin Stimulation Test. The treatment effect refers to the comparison of hydrocortisone+fludrocortisone versus hydrocortisone alone or placebo.

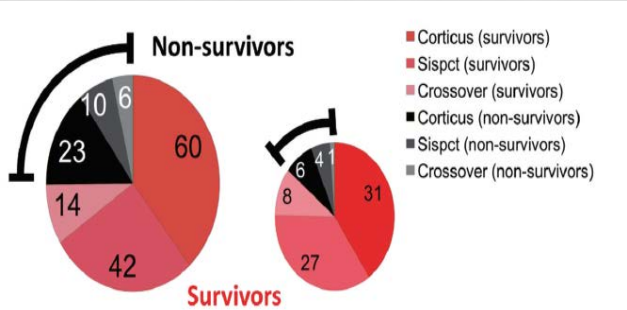
IPD Meta-analysis from 3 large RCTS
Ger-Inf (Jama 2002, n=300); corticus (NEJM 2008, n=500); coiittss (Jama 2010 n=500)

Pirracchio, unpublished

IMMUNE STATUS

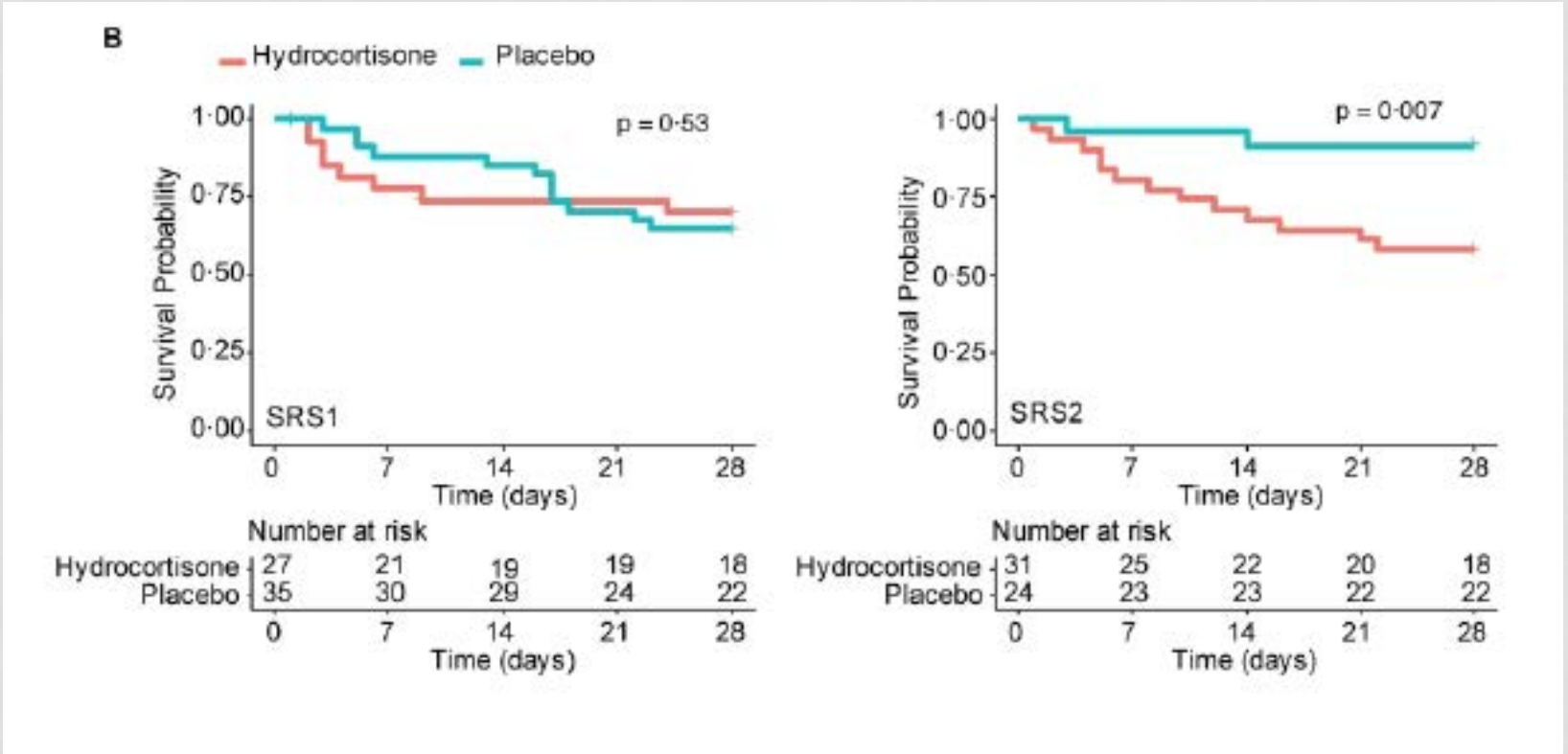






With permission, Briegel, Bauer & Keh

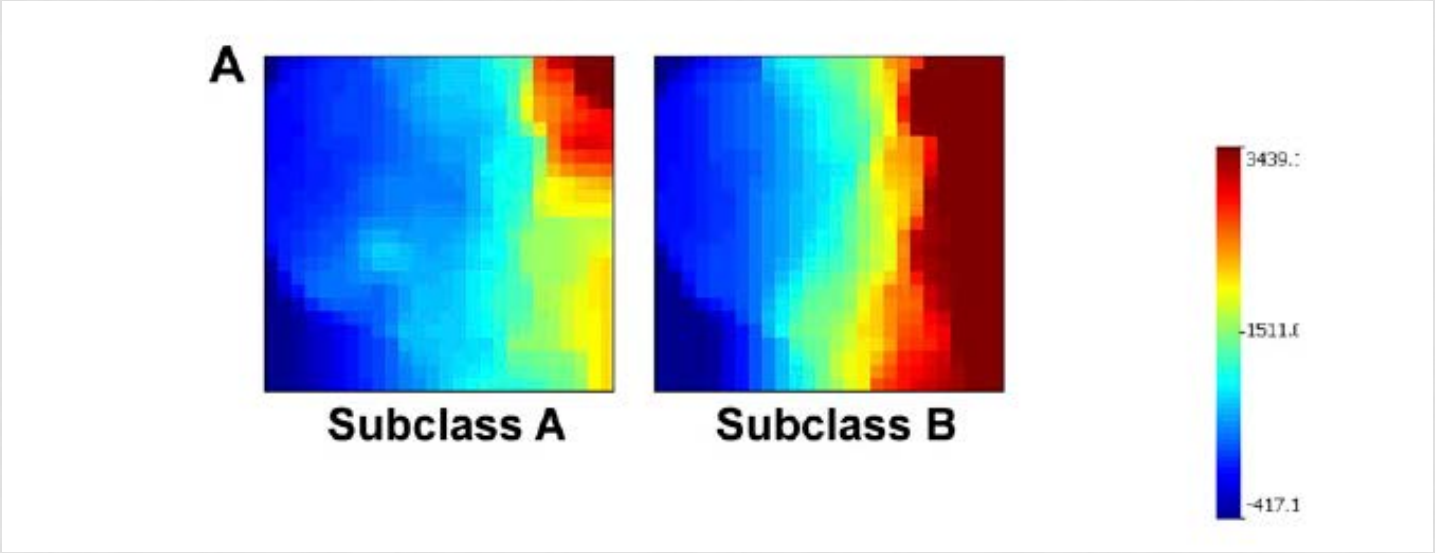
OMICS CORTICOSTEROIDS RESPONSE SIGNATURE



SRS1: immune suppressed
SRS2: immune competent

Antcliffe AJRCCM 2018

OMICS CORTICOSTEROIDS RESPONSE SIGNATURE



CS:52/120 CS:104/180

OR death: 4.1 (1.4-12) OR death: 3.9 (0.8-18)

Subclass A: immune suppressed
Subclass B: immune competent

Wong AJRCCM 2014

EN PRATIQUE – JE RETIENS LA RÈGLE DES 4 « P » :TRAITER

- Par
  - hydrocortisone (50mg q6) +
  - fludrocortisone (50µg q24)
- Pendant
  - 7 jours
  - Sans décroissance
- Pour
  - Choc septique,
  - Sepsis + ARDS,
  - Sepsis sur PCA
- Pas
  - répondeurs au test à ACTH, ie delta cortisol>9µg/dl