Corticostéroïdes et trauma crânien

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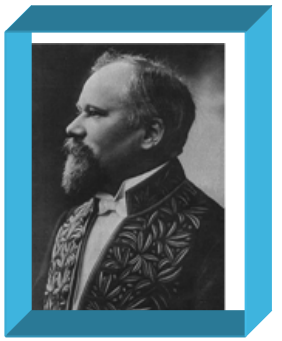
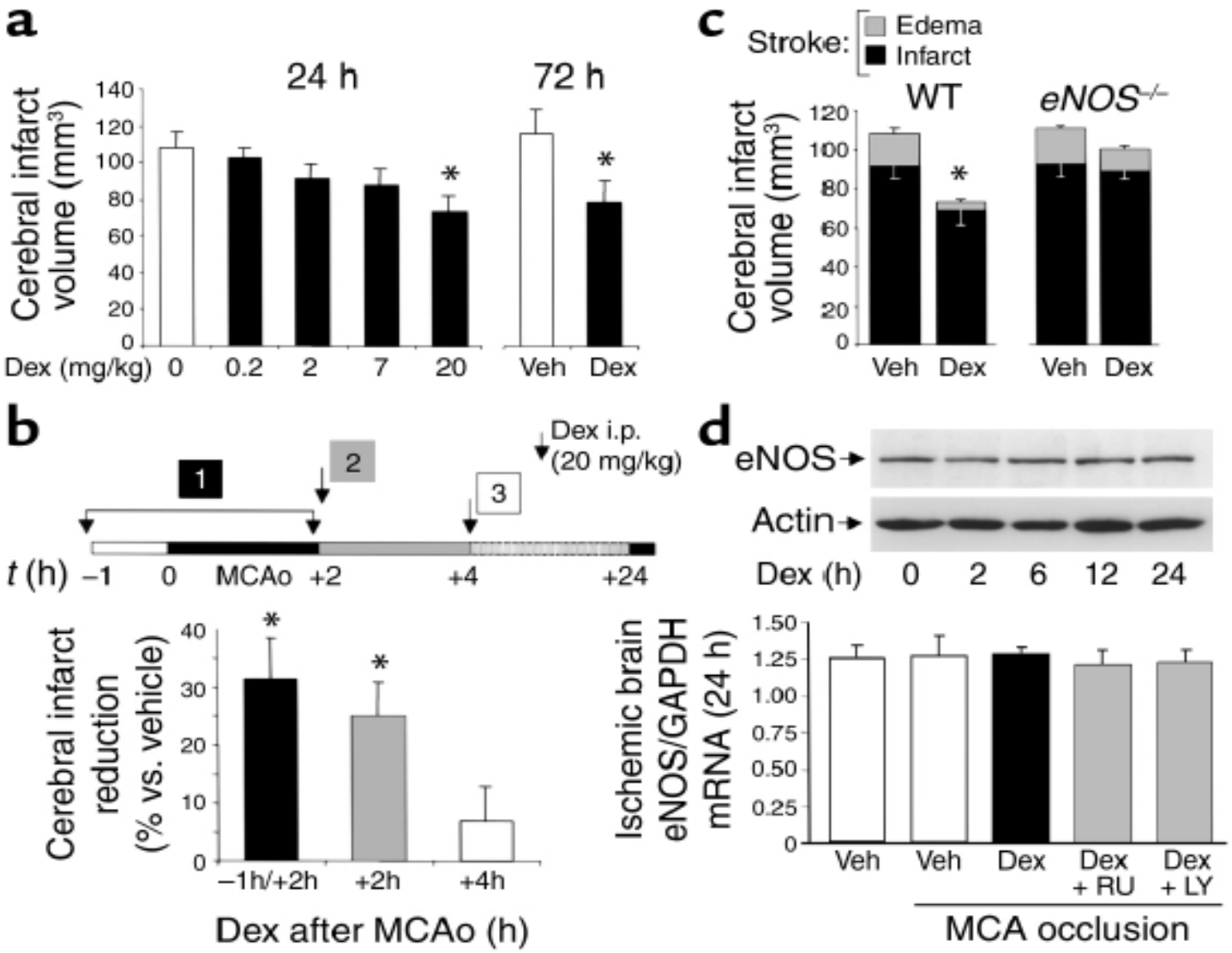


Rationnel

Neuroprotection induite par la corticothérapie



Limbourg JCI 2002

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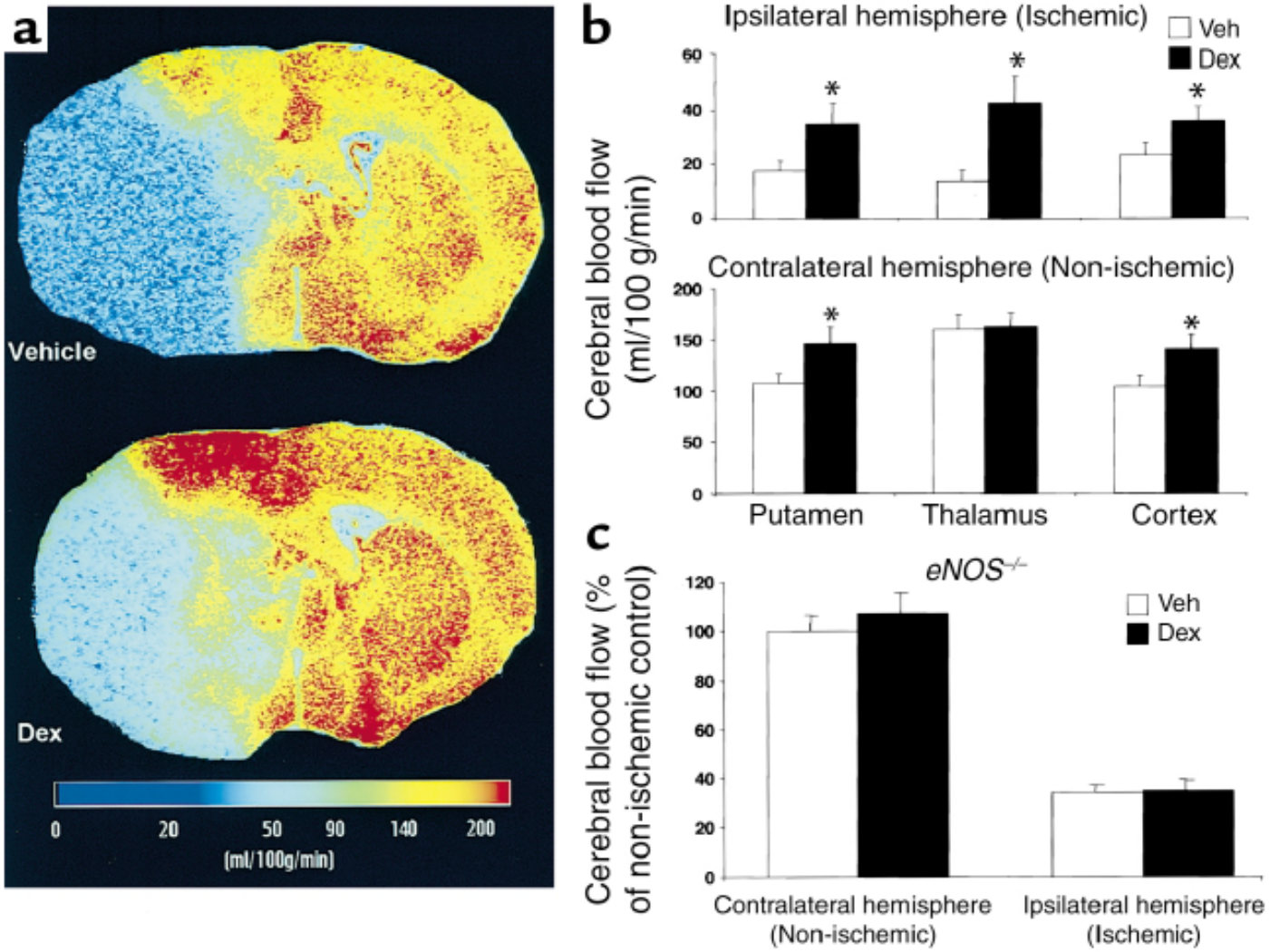

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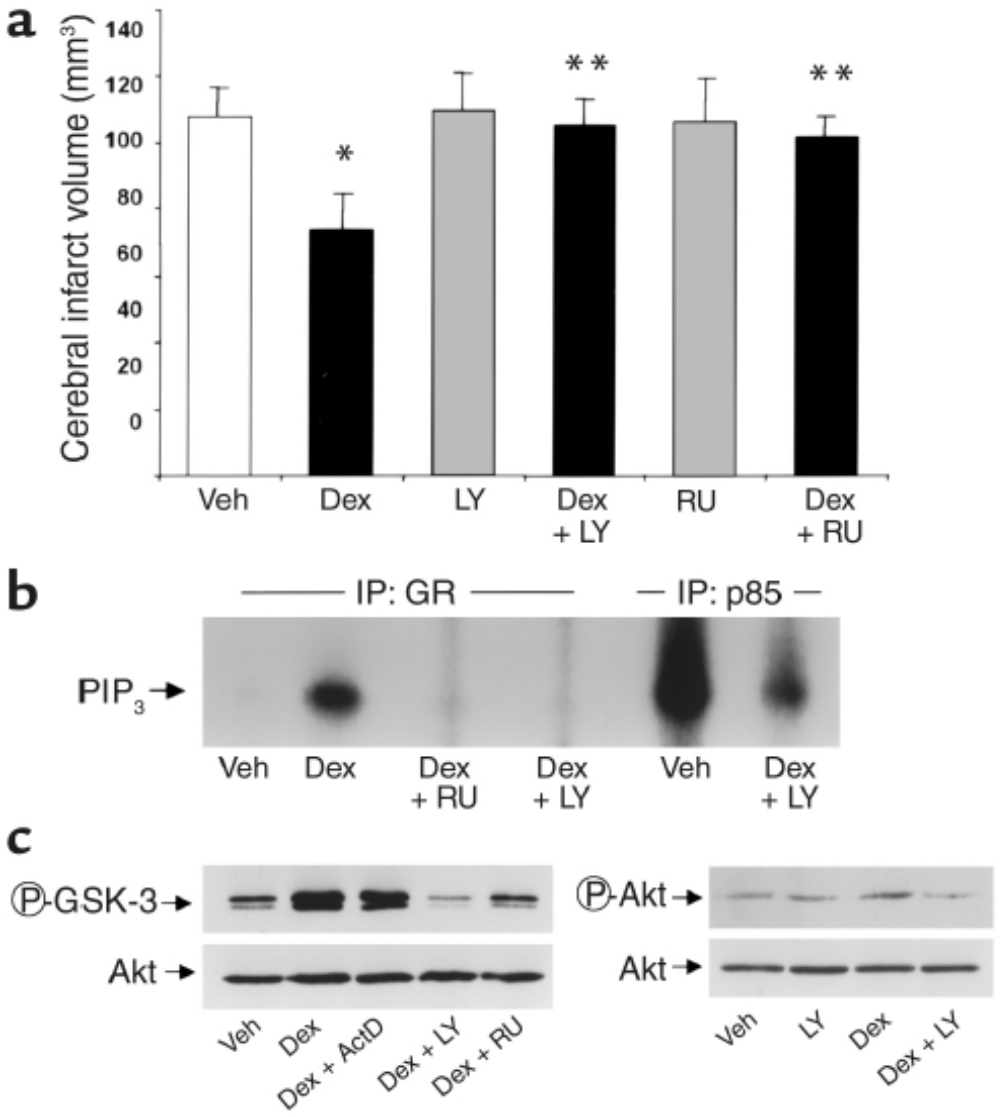

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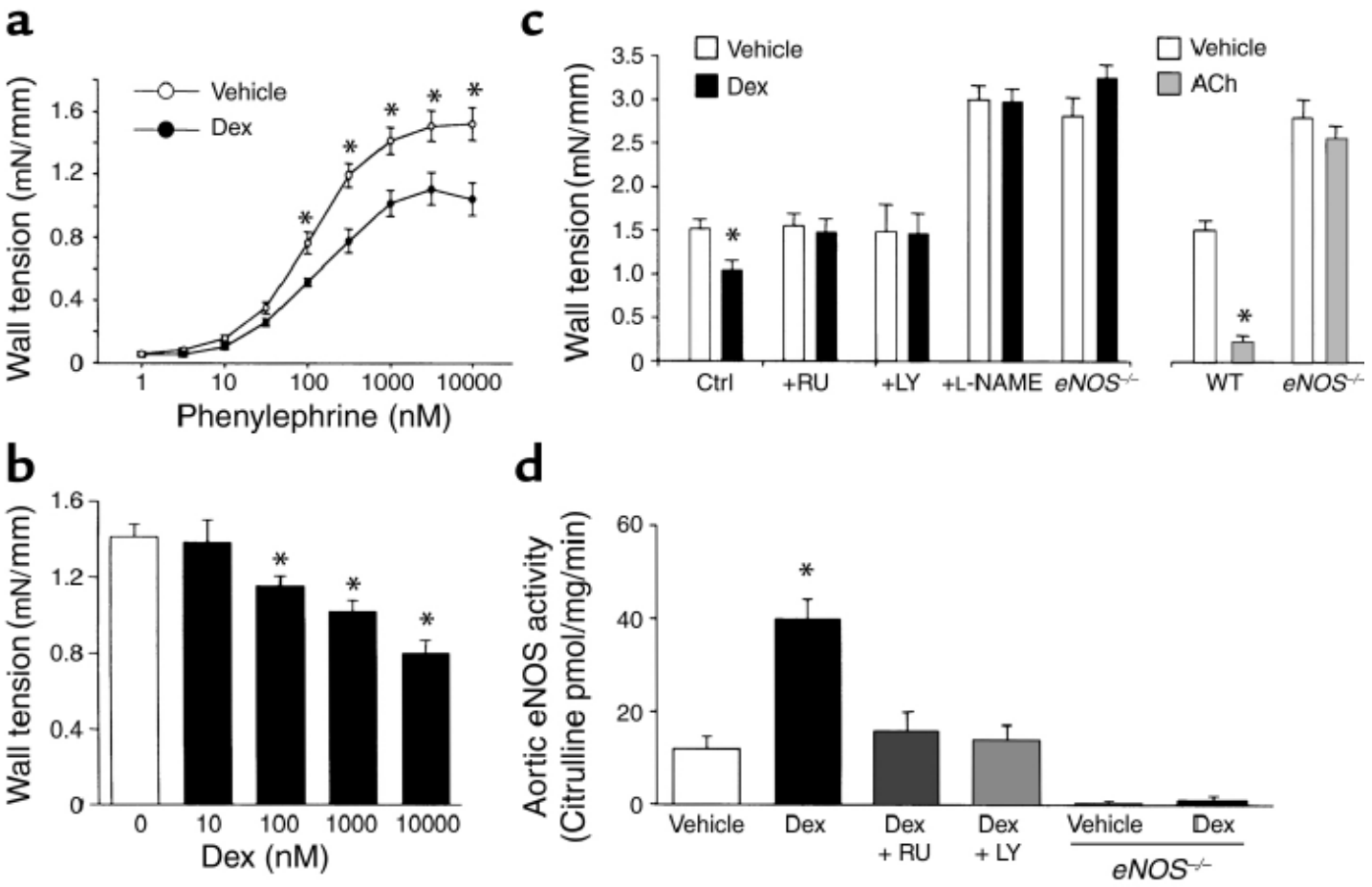

Limbourg JCI 2002

Anesthesiology 2002; 97:807-13

Cortisol Response to Corticotropin Stimulation in Trauma Patients

Influence of Hemorrhagic Shock

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- 34 patients traumatisés
- Critères d'inclusion: (1) 18 ans ≤ âge ≤ 55 ans; (2) ISS >16; (3) Survie > 48 h.
- Critères d'exclusion: Grossesse; Comorbidités associées (axe HHS)
- Cortisolémie basale < 18 μg/dL: 56%
- Test ACTH (Δcortisolémie < 9 μg/dL): 47% (n = 16)
- Corrélation réponse test ACTH/cortisolémie NS (cortisolémie de base répondeurs vs non répondeurs: 18 ± 9 vs 18 ± 8 μg/dL)

Hoen S et al. Anesthesiology 2002

Table 2. Clinical and Biologic Characteristics of the Patients according to the Cortisol Response (ΔCort) to Corticotropin Stimulation at the End of the Early Phase

	Early Responder ΔCort ≥ 9 μg/dl	Early Nonresponder ΔCort < 9 μg/dl	*P* Value
Time to early stimulation (h)	23.9 ± 15.3	19.1 ± 13.0	0.333
n	18	16	
Age (yr)	35.9 ± 12.1	30.9 ± 12.6	0.244
Gender (M/F)	12/6	14/2	0.233
Time to admission (h)	2.5 ± 1.2	4.2 ± 3.3	0.057
Injury Severity Score	27.6 ± 7.1	30.9 ± 7.3	0.195
SAPS II	34.3 ± 12.7	39.4 ± 15.4	0.436
Etomidate administration	12	9	0.725
Hemorrhagic shock	5	11	0.037
Peak arterial lactate	2.2 ± 1.5	3.9 ± 1.7	0.003
Early MOD score	4.6 ± 2.7	7.6 ± 2.9	0.004
Total volume loading (ml)	8,011 ± 6,412	10,297 ± 7,600	0.349
Volume loading rate (ml/h)	409 ± 434	583 ± 344	0.022
Crystalloid volume (ml)	4,489 ± 3,194	4,066 ± 3,067	0.697
Colloid volume (ml)	1,975 ± 2,062	3,356 ± 1,724	0.043
No. of patients transfused	9	11	0.315
Blood product volume (ml)	1,547 ± 2,174	2,813 ± 3,297	0.191
Norepinephrine infusion	11	12	0.324
Mechanical ventilation	11	13	0.270
Plasma total proteins (g/l)	46.6 ± 11.5	44.1 ± 9.2	0.484
Interleukin-6 (pg/ml)	311 ± 466	728 ± 589	0.048

MOD = multiple organ dysfunction.

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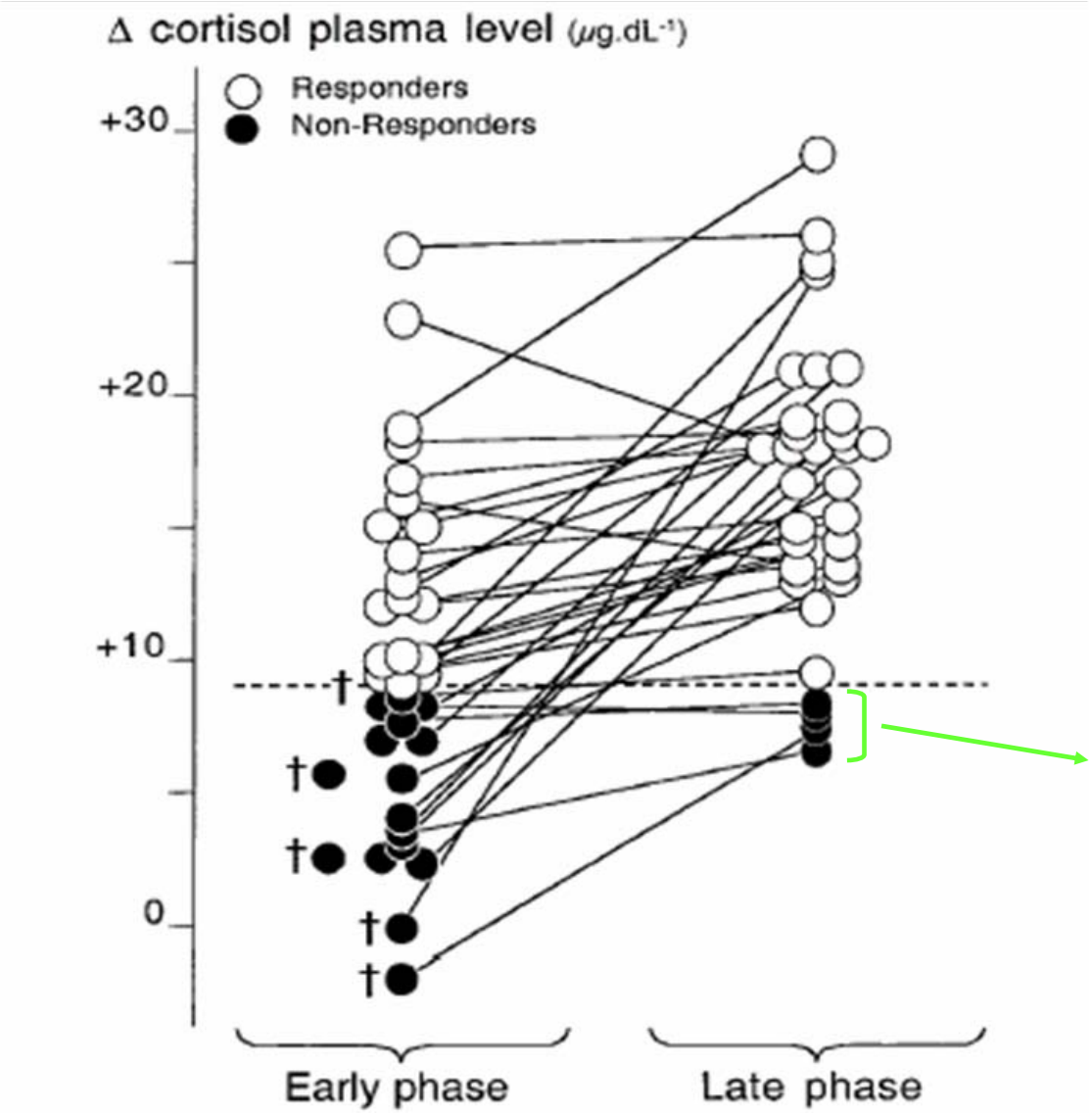

25% of the Non-responders

Fig. 1. Cortisol response to corticotropin stimulation at the end of the early phase (21.7 ± 14.3 h) and at the end of the first posttraumatic week (late phase; 156.5 ± 52.2 h). The dashed line represents the threshold of normal response (+9 g/dl), and daggers indicate the nonsurvivors.

Hoen S et al. Anesthesiology 2002

Table 3. Influence of the Cortisol Response (ΔCort) to Corticotropin Stimulation during the Early Phase on the Response to the Second Stimulation (Late Phase) and the Overall Outcomes

	Early Responder ΔCort ≥ 9 μg/dl	Early Nonresponder ΔCort < 9 μg/dl	*P* value
Time to late stimulation (h)	152.1 ± 64.0	162.2 ± 37.9	0.607
Late MOD score	2.6 ± 2.5	3.4 ± 3.9	0.518
Plasma total proteins (g/l)	54.5 ± 5.5	52.9 ± 7.1	0.466
Basal cortisol value (μg/dl)	18.1 ± 5.0	19.6 ± 8.5	0.518
Δ Cortisol value (μg/dl)	+17.8 ± 4.8	+14.9 ± 5.9	0.138
No. of infectious episodes	1.9 ± 2.5	2.3 ± 2.6	0.660
Norepinephrine treatment			
Duration (h)	51.3 ± 112.0	84.6 ± 103.1	0.040
Total dose (mg)	30.0 ± 62.1	123.2 ± 245.2	0.038
ICU length of stay (days)	15.8 ± 11.7	18.0 ± 16.4	0.650
ICU death (mortality)	1 (6%)	4 (25%)	0.164
Hospital length of stay (days)	50.2 ± 44.0	47.7 ± 54.3	0.584

MOD = multiple organ dysfunction; ICU = intensive care unit.

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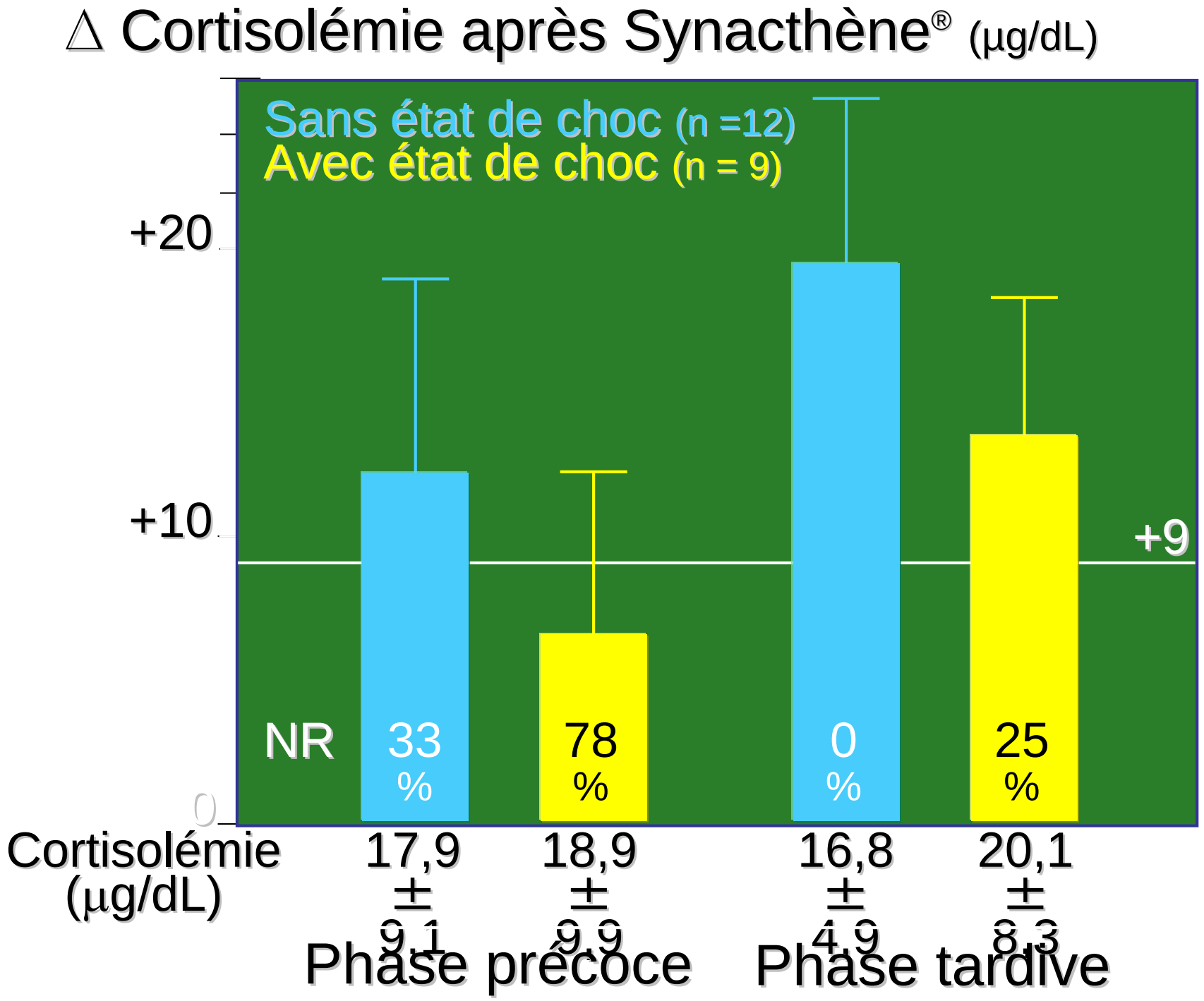
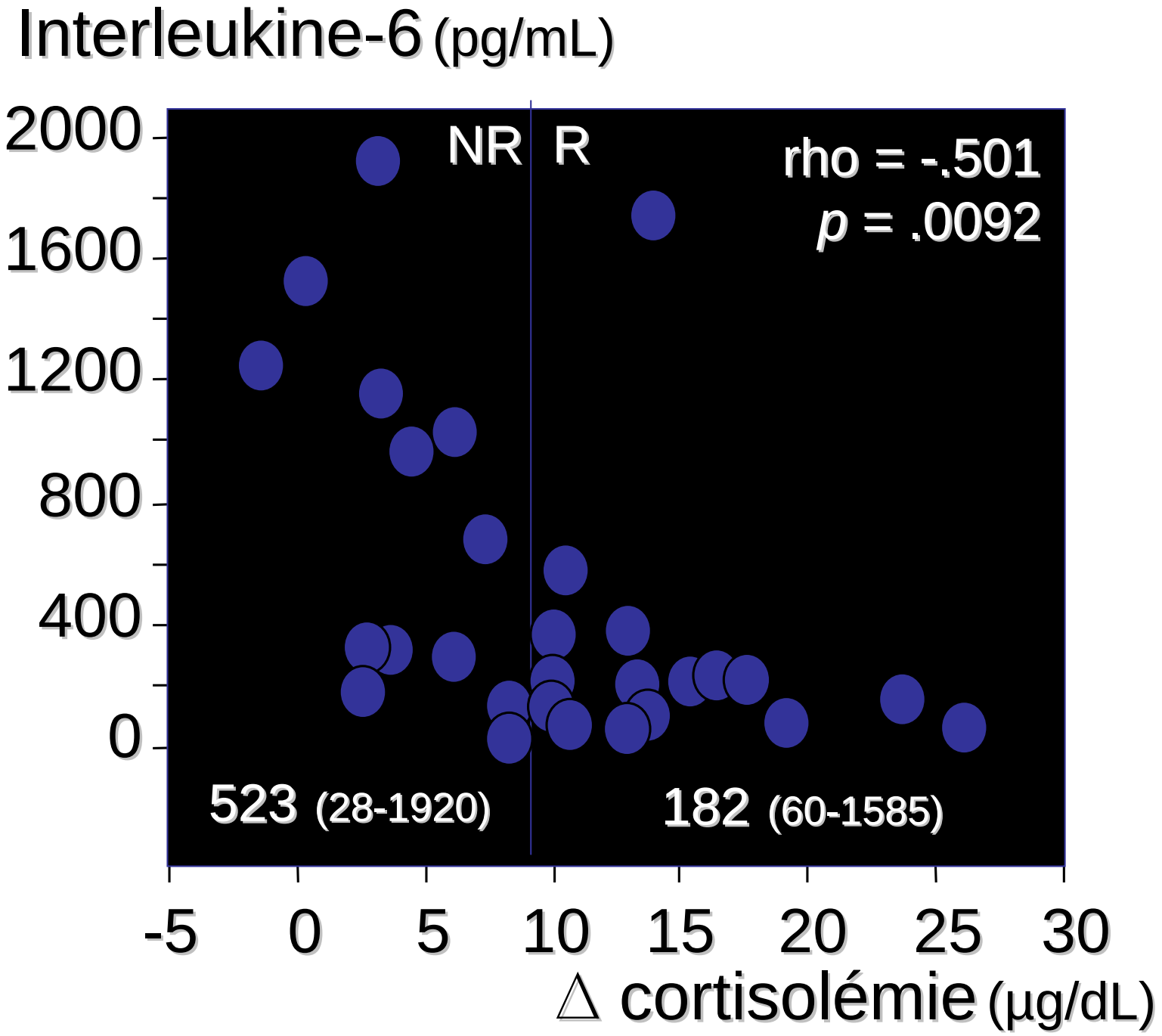
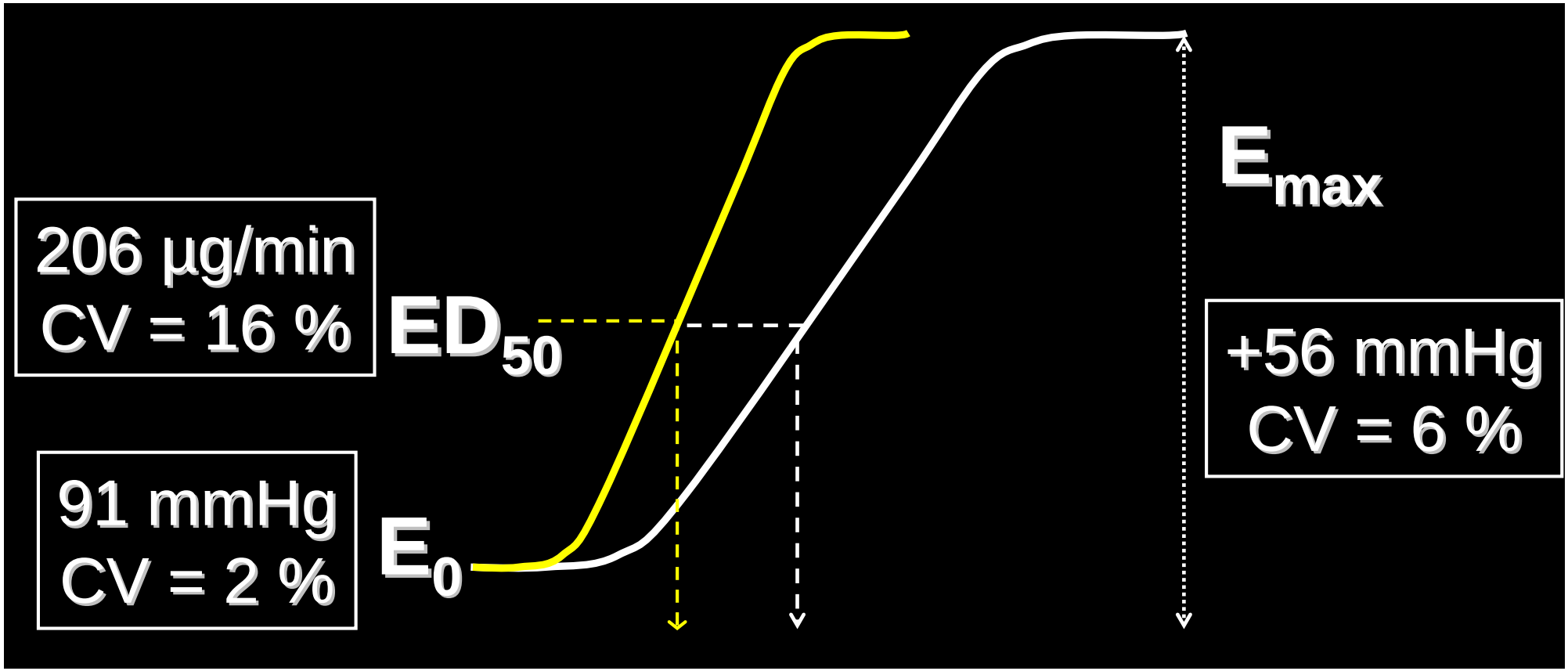


Hoen S et al. Anesthesiology 2002



Asehnoune K et al. SFAR 2002; R37

Chez les blessés avec état de choc à l'admissio
quelle que soit la réponse à l'ACTH



Δ ED_{50} = -30 % après hydrocortisone

Hydrocortisone Therapy for Patients With Multiple Trauma

The Randomized Controlled HYPOLYTE Study

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Context The role of stress-dose hydrocortisone in the management of trauma patients is currently unknown.

Objective To test the efficacy of hydrocortisone therapy in trauma patients.

Design, Setting, and Patients Multicenter, randomized, double-blind, placebo-controlled HYPOLYTE (Hydrocortisone Polytraumatise) study. From November 2006 to August 2009, 150 patients with severe trauma were included in 7 intensive care units in France.

Intervention Patients were randomly assigned to a continuous intravenous infusion of either hydrocortisone (200 mg/d for 5 days, followed by 100 mg on day 6 and 50 mg on day 7) or placebo. The treatment was stopped if patients had an appropriate adrenal response.

Main Outcome Measure Hospital-acquired pneumonia within 28 days. Secondary outcomes included the duration of mechanical ventilation, hyponatremia, and death.

Results One patient withdrew consent. An intention-to-treat (ITT) analysis included the 149 patients, a modified ITT analysis included 113 patients with corticosteroid insufficiency. In the ITT analysis, 26 of 73 patients (35.6%) treated with hydrocortisone and 39 of 76 patients (51.3%) receiving placebo developed hospital-acquired pneumonia by day 28 (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.30-0.83; $P=.007$). In the modified ITT analysis, 20 of 56 patients (35.7%) in the hydrocortisone group and 31 of 57 patients (54.4%) in the placebo group developed hospital-acquired pneumonia by day 28 (HR, 0.47; 95% CI, 0.25-0.86; $P=.01$). Mechanical ventilation–free days increased with hydrocortisone by 4 days (95% CI, 2-7; $P=.001$) in the ITT analysis and 6 days (95% CI, 2-11; $P<.001$) in the modified ITT analysis. Hyponatremia was observed in 7 of 76 (9.2%) in the placebo group vs none in the hydrocortisone group (absolute difference, –9%; 95% CI, –16% to –3%; $P=.01$). Four of 76 patients (5.3%) in the placebo group and 6 of 73 (8.2%) in the hydrocortisone group died (absolute difference, 3%; 95% CI, –5% to 11%; $P=.44$).

Conclusion In intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia.

Trial Registration clinicaltrials.gov Identifier: NCT00563303

JAMA. 2011;305(12):1201-1209 www.jama.com

SEVERE TRAUMA IS ONE OF THE leading causes of death and morbidity in the world.[1] The overall rate of posttraumatic pneumonia reaches an incidence of 40% to 60%, mainly in patients with traumatic brain injury (TBI).[2-4] Early posttraumatic pneumonia increases the duration of mechanical ventilation, hospitalization,[5] and risk of death. Thus, prevention of posttrauma pneumonia is a major clinical and economical issue.

Stress-dose hydrocortisone was suggested as a means of improving outcome in septic patients with critical illness–related corticosteroid insufficiency.[6] Recommendations advocate the use of long-term stress-dose hydrocortisone (200 mg/d) in patients with septic shock[7]

For editorial comment see p 1242.

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JAMA®
The Journal of the American Medical Association

Published March 23, 2011

Available at www.jama.com

Objective

To test the efficacy of hydrocortisone therapy in trauma patients with corticosteroid insufficiency

- **Main outcome measure** Ocurrence of hospital-acquired pneumonia (HAP) within 28 days
- **Secondary outcomes:**
  - time-to-mechanical-ventilation withdrawal, length of ICU stay
  - Other nosocomial infections, Organ failure
  - Death rate
  - Safety

Material et methods

✓ Fundings: grant from the French ministry of Health (PHRC 2006)

✓ **Study design**

- Multicentric (7 ICU)
- Randomized (ratio 1/1, stratified on center, TBI, and ISS)
- Controled versus placebo
- Double Blind
- Parallel arms

Material et methods: Design

✓ **Short corticotropin test**

✓ **Treatment started in the first 36 hrs following trauma**

- **Hydrocortisone continuously intravenously:** 200 mg/day
- **Placebo**

✓ **Adapted corticosteroid function:**

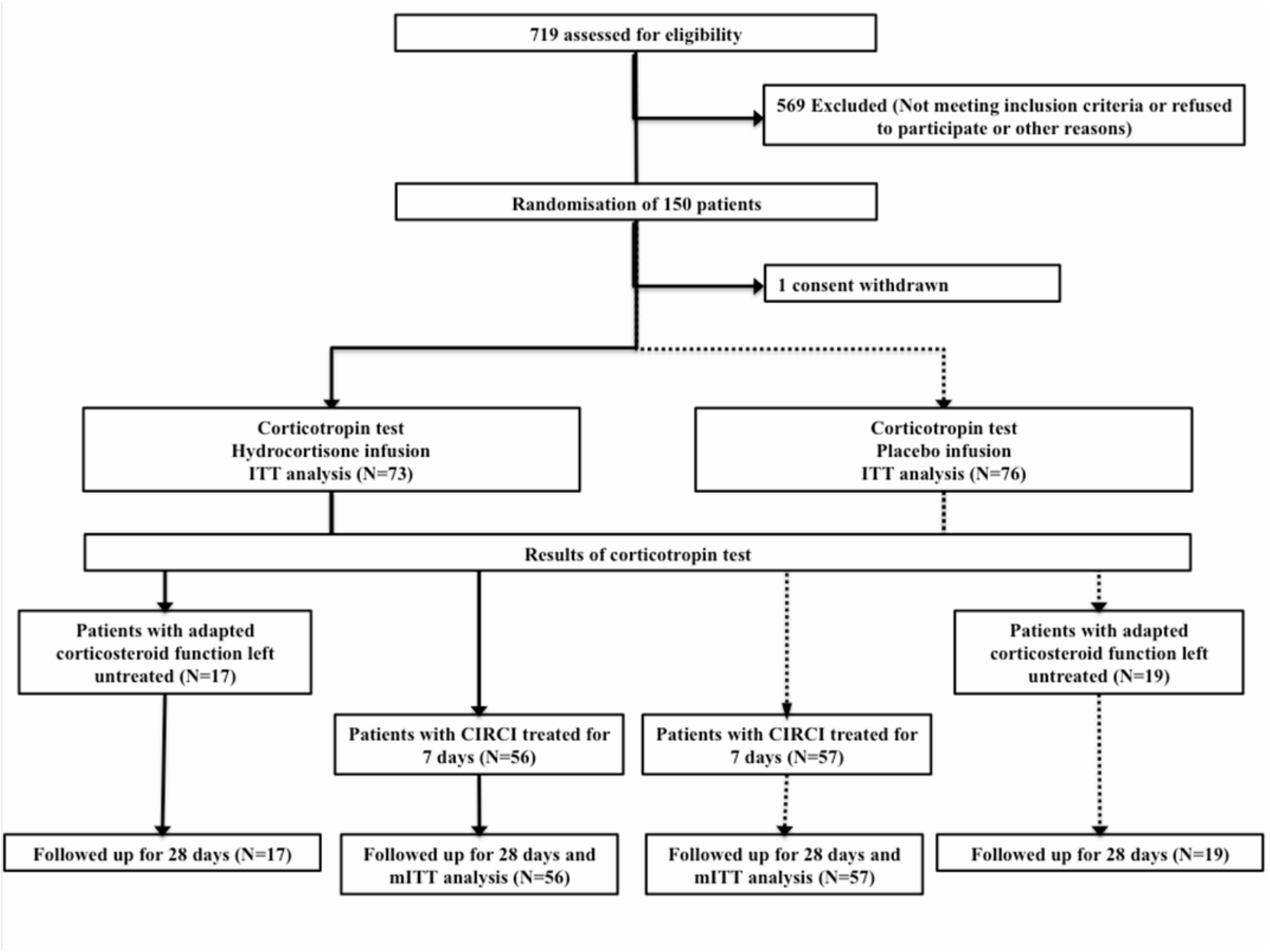
- **Treatment was stopped** After receiving the results of the short corticotropin test (in the first 48 hours following inclusion),

✓ **Patients with CIRCI**

- the study drugs were continuously administered intravenously as follows: 200 mg/day for 5 days, 100 mg on day 6, and 50 mg on day 7

RESULTS

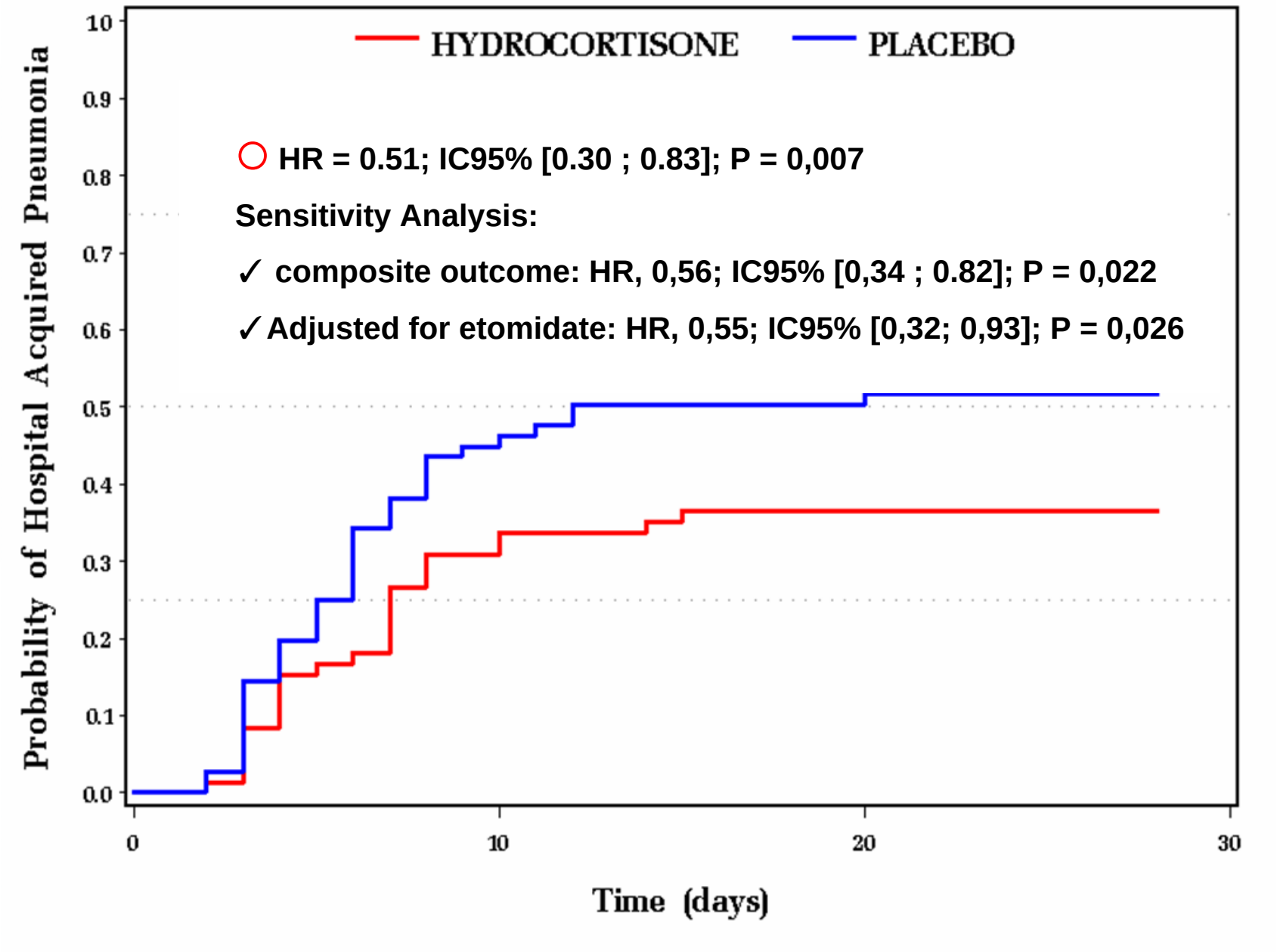
Flow Chart


719 assessed for eligibility
569 Excluded (Not meeting inclusion criteria or refused to participate or other reasons)
Randomisation of 150 patients
1 consent withdrawn
Corticotropin test
Hydrocortisone infusion
ITT analysis (N=73)
Corticotropin test
Placebo infusion
ITT analysis (N=76)
Results of corticotropin test
Patients with adapted corticosteroid function left untreated (N=17)
Patients with CIRCI treated for 7 days (N=56)
Patients with CIRCI treated for 7 days (N=57)
Patients with adapted corticosteroid function left untreated (N=19)
Followed up for 28 days (N=17)
Followed up for 28 days and mITT analysis (N=56)
Followed up for 28 days and mITT analysis (N=57)
Followed up for 28 days (N=19)

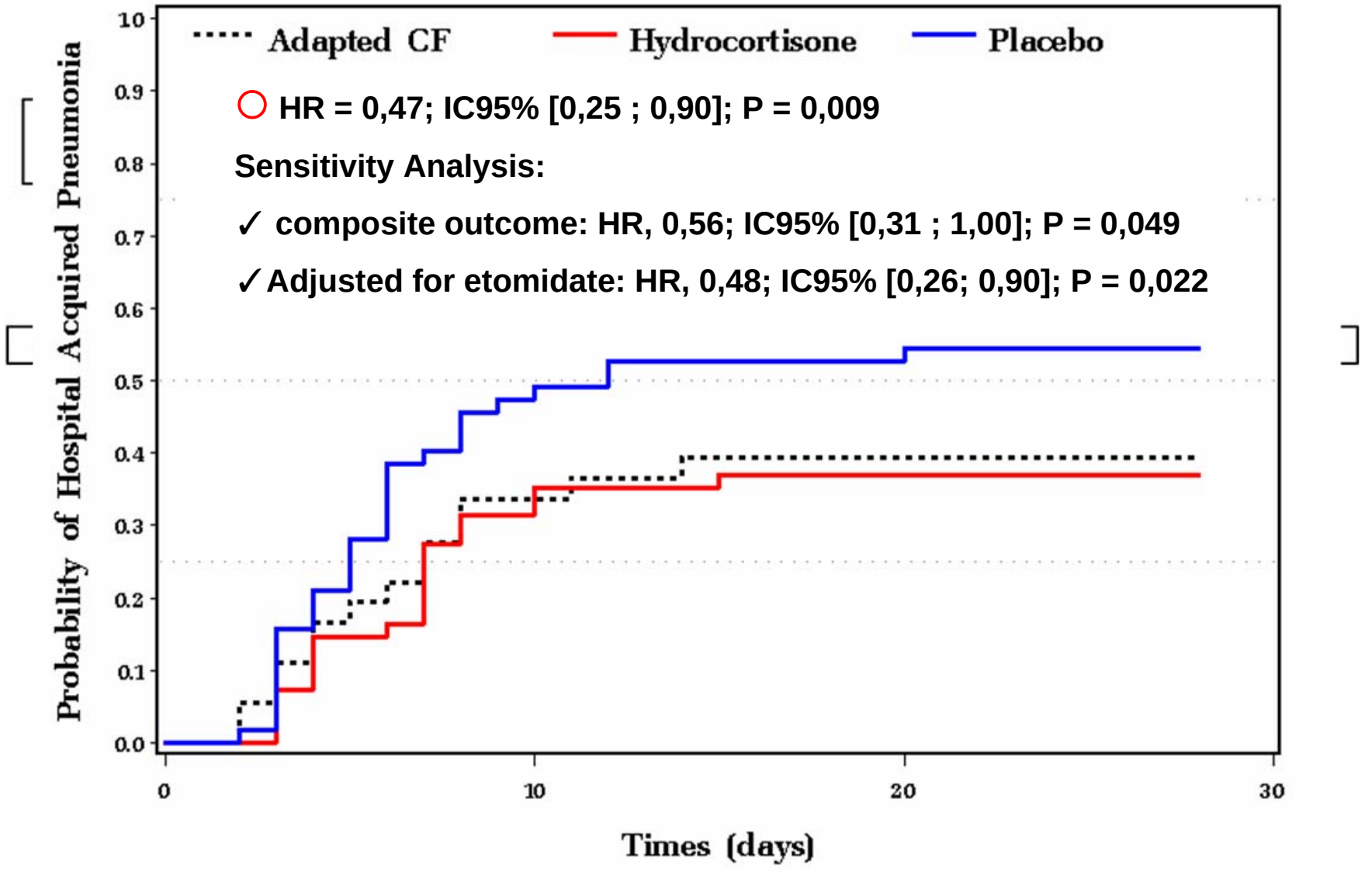
Results: population

	CIRCI Patients		Adapted function (n=36)
	Hydrocortisone (n=56)	Placebo (n=57)	
Age (years) – mean ± DS	35,2±17,3	34,9±18,0	40,8±17,9
Male – no. (%)	42 (75,0)	47 (82,5)	28 (77,8)
Traumatic brain Injury – no. (%)	32 (57,1)	35 (61,4)	17 (47,2)
ISS – median (IQ)	30 (22-36)	30 (22-38)	27 (22-34)
Fluid infusion prior to inclusion – mediane (IQ)			
Red cells units	5 (2-9)	4 (0-9)	4 (0-11)
Norepinephrine (μ g/kg/min)	0,3 (0,2-0,5)	0,3 (0,2-0,5)	0,2 (0,1-0,4)
Duration between (min) – median (IQ)			
Traumatism and tracheal intubation	57 (20-120)	60 (35-150)	60 (30-360)
Tracheal intubation and cosyntropin test	1275 (950-1525)	1410 (1165-1710)	1370 (1140-1750)
Cosyntropin test (μ g/dl) – median (IQ)			
Basal Cortisolemia	19,6 (11,7-28,3)	16,0 (10,5-27,2)	21,2 (18,2-25,8)
Delta after 30 minutes	3,5 (1,9-9,2)	4,6 (0,9-12,3)	10,8 (7,9-13,0)
Delta after 60 minutes	6,3 (2,5-12,7)	6,5 (2,3-15,6)	14,6 (11,2-17,1)

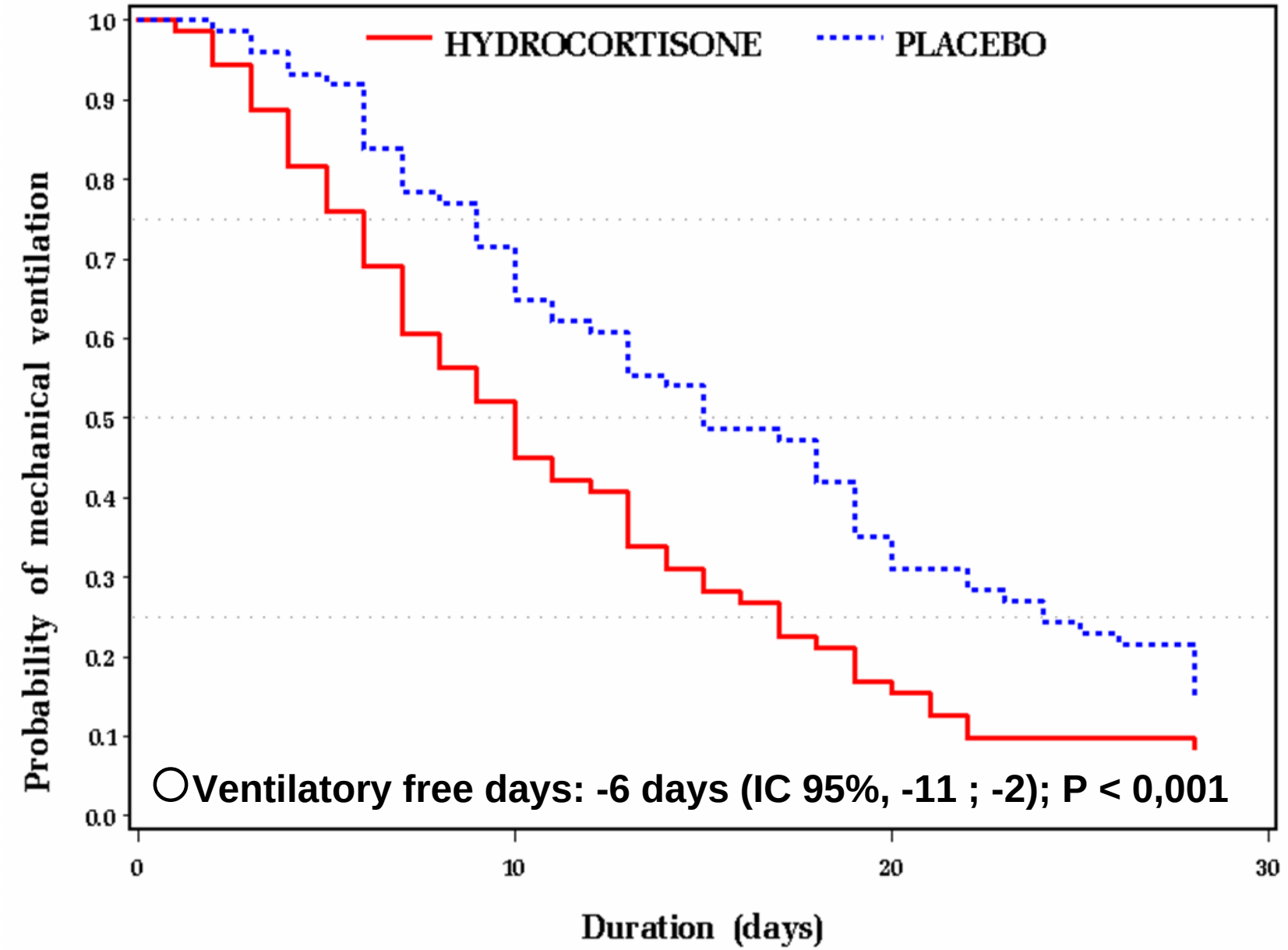
Results: Nosocomial pneumonia within Day 28 all patients (ITT)



Results: Nosocomial pneumonia within Day 28 CIRCI patients (mITT)

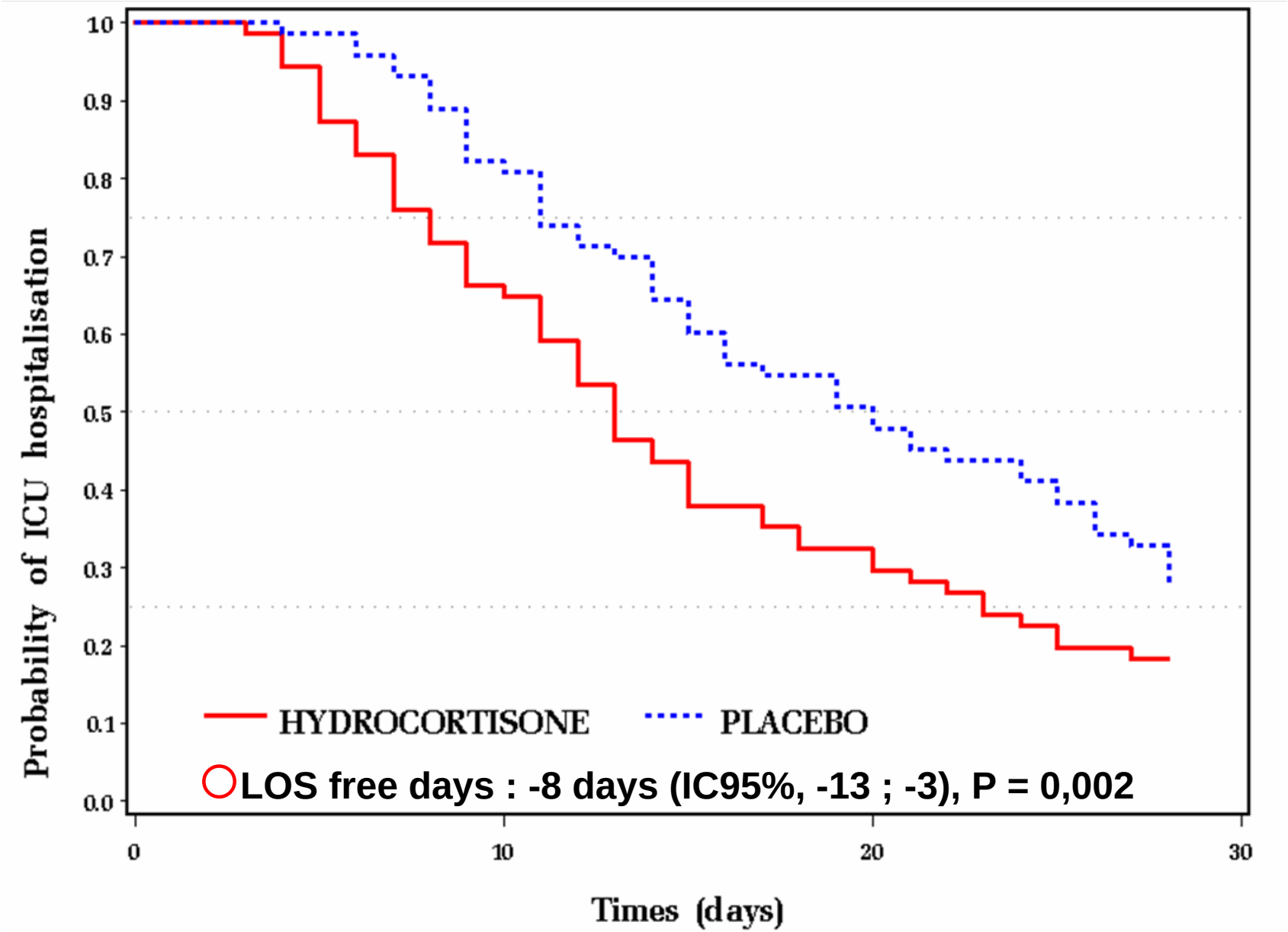


Ventilatory free days

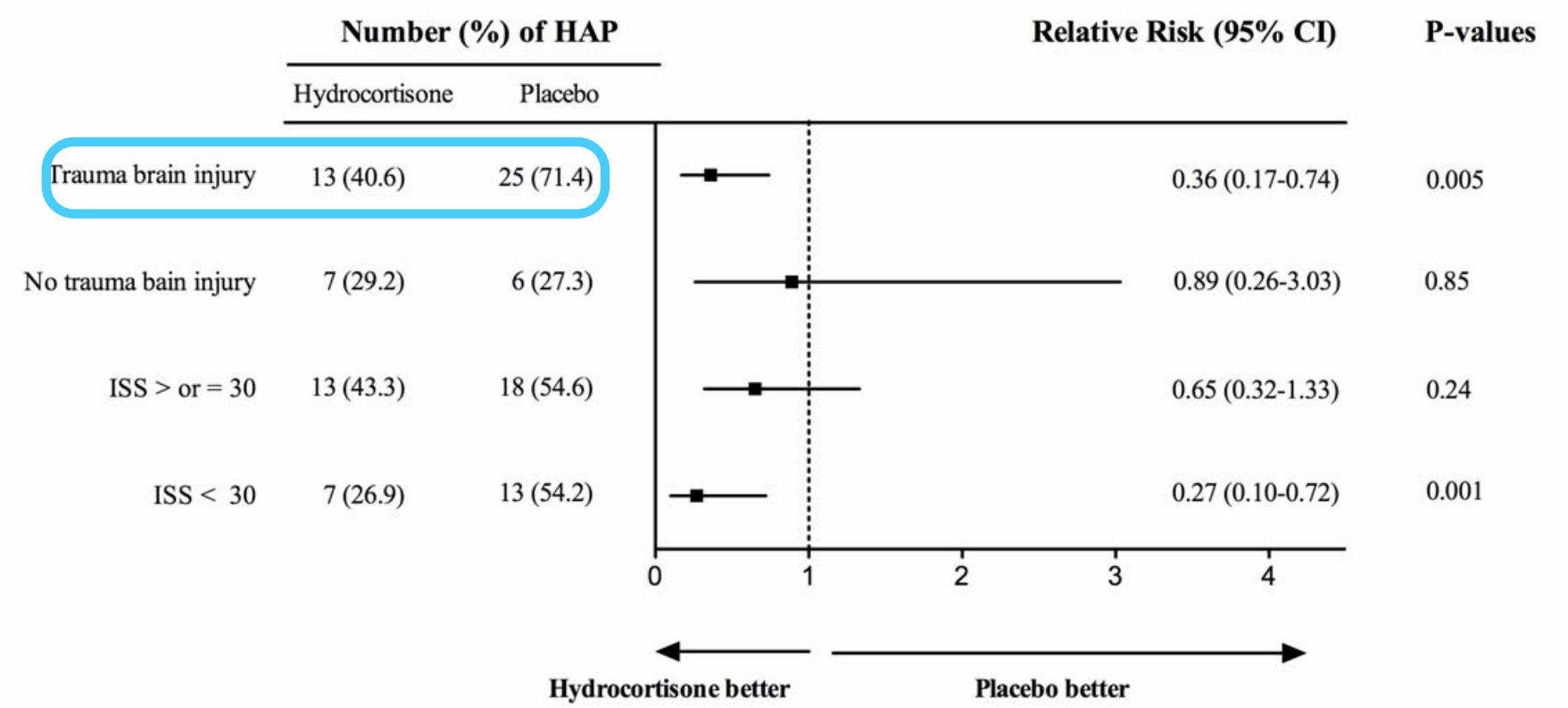


○Ventilatory free days: -6 days (IC 95%, -11 ; -2); P < 0,001

Length of stay in ICU



Résults: Nosocomial pneumonia within Day 28 sub group (mITT)



Safety

	CIRCI patients			Adapted function (n=36)	P value**	P value***
	Hydrocortisone (n=56)	Placebo (n=57)	P value*			
Metabolic complications – no. (%)						
Hyperglycemia (≥180 mg/dl)	5 (8,9)	3 (5,3)	0,44	2 (5,7)	0,85	0,76
Hyperkaliemia (≥ 5,0 mmol/l)	2 (3,6)	3 (5,3)	0,71	1 (2,9)	0,91	0,81
Hypernatremia (≥150 mmol/l)	7 (12,5)	6 (10,5)	0,69	4 (11,4)	0,79	0,74
Hypokaliemia (≤3,0 mmol/l)	5 (8,9)	3 (5,3)	0,43	1 (2,9)	0,68	0,35
Hyponatremia (≤130 mmol/l)	0 (0,0)	7 (12,3)	0,008	0 (0,0)	0,09	/
Gastro-intestinal bleeding Or perforation – no. (%)	1 (1,8)	0 (0,0)	0,31	0 (0,0)	/	0,65

* Hydrocortisone versus Placebo ; ** Placebo versus adapted function ; *** Hydrocortisone versus adapted function

Modifiable factors of HAP

Interventions	all patients (ITT)			CIRCI patients (mITT)			Adapted corticosteroid function (n=36)	P-values**	P-values***
	Hydrocortisone (n=73)	Placebo (n=76)	P-value	Hydrocortisone (n=56)	Placebo (n=57)	P-values*			
Antibiotic prophylaxis **– no. (%)**	63 (86.3)	65 (85.5)	0.89	49 (87.5)	50 (87.7)	0.97	29 (80.6)	0.35	0.37
Duration of antibiotic prophylaxis (days) – median (IQR)	5 (2-6)	4.5 (2-6)	0.97	5 (2-6)	5 (2-6)	0.51	3 (2-6)	0.69	0.95
Oropharyngeal decontamination – no. (%)	44 (61.1)	47 (61.8)	0.93	32 (57.1)	36 (63.2)	0.51	23 (65.7)	0.80	0.42
Enteral nutrition at day 7 – no. (%)	64 (88.9)	69 (90.8)	0.70	49 (87.5)	53 (93.0)	0.33	31 (88.6)	0.47	1
Stomach ulcer prevention – no. (%)	43 (59.7)	56 (73.7)	0.07	37 (66.1)	41 (71.9)	0.50	21 (60.0)	0.24	0.56
Proclive > 30° – no. (%)	62 (87.3)	67 (88.2)	0.88	48 (87.3)	50 (87.7)	0.94	31 (88.6)	1	1
Protocol for glycemia control – no. (%)	68 (94.4)	71 (94.7)	1	55 (98.2)	52 (92.9)	0.36	32 (91.4)	1	0.16

Mortality

	All patients (ITT)		CIRCI patients (mITT)		Adapted corticosteroid function
	Hydrocortisone (n=73)	Placebo (n=76)	Hydrocortisone (n=56)	Placebo (n=57)	(n=36)
N					
Cause of death					
Hemorrhage or intracranial hypertension	2	2	2	1	1
Trauma and infection	3	2	3	2	0
Withdrawing of life sustaining therapies	1	0	1	0	0
Timing of death					
Death < 48 hours (hemorrhage or intracranial hypertension)	2	1	2	0	1
2 days < Death < 28 days	4	3	4	3	0

Corticosteroids function at day 8

	CIRCI patients			
	Hydrocortisone (n=56)	**Placebo (n=57)**	**Absolute difference [IC 95%]**	**P value**
Corticosteroids insufficiency – no. (%)	25 (62,5)	17 (33,3)	-29 [-49 ; -9]	<0,001
Basal cortisolemia (μ g/dl) – median (IQ)	19,5 (15,6-25,6)	22,0 (15,0-29,3)	-1,9 [-6,1 ; 2,4]	0,39
Delta after 30 min (μ g/dl) – median (IQ)	7,8 (3,6-11,2)	13,0 (8,7-18,5)	-5,8 [-83,2 ; -3,3]	<0,001
Delta after 60 min (μ g/dl) – median (IQ)	10,0 (5,2-15,1)	16,7 (13,1-23,4)	-6,2 [-10,7 ; -1,7]	0,01

Conclusion

- ✓ Environ 40 à 60% des patients polytraumatisés, en particuliers avec traumatisme crânien ont une insuffisance surrénale relative
- ✓ Doses modérées (200 mg/jour) d'hydrocortisone pendant une semaine réduit le risque de PAVM chez le patient polytraumatisé
- ✓ L'effet semble encore plus marqué en cas de traumatisme crânien
- ✓ Le traitement est bien toléré; néanmoins on note un risque important d'insuffisance surrénale à l'arrêt du traitement, suggérant un traitement plus long et/ou une décroissance plus lente

Corti-TC

Corticosteroid Therapy for Glucocorticoid Insufficiency Related to Traumatic Brain Injury

NCT01093261