

Les grands essais thérapeutiques dans le sepsis

Pr B Levy

Nancy

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

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Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

Table 1. Grading system

Grading of recommendations

- A. Supported by at least two level I investigations
- B. Supported by one level I investigation
- C. Supported by level II investigations only
- D. Supported by at least one level III investigation
- E. Supported by level IV or V evidence

Grading of evidence

- I. Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error
 - II. Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
 - III. Nonrandomized, contemporaneous controls
 - IV. Nonrandomized, historical controls and expert opinion
 - V. Case series, uncontrolled studies, and expert opinion
-

Early Goal directed therapy

■ Grade B

Goals



- Central venous pressure (CVP) 8–12 mmHg
- Mean arterial pressure (MAP) ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg h⁻¹
- Central venous (superior vena cava) or mixed venous oxygen saturation $\geq 70\%$.

Grade B

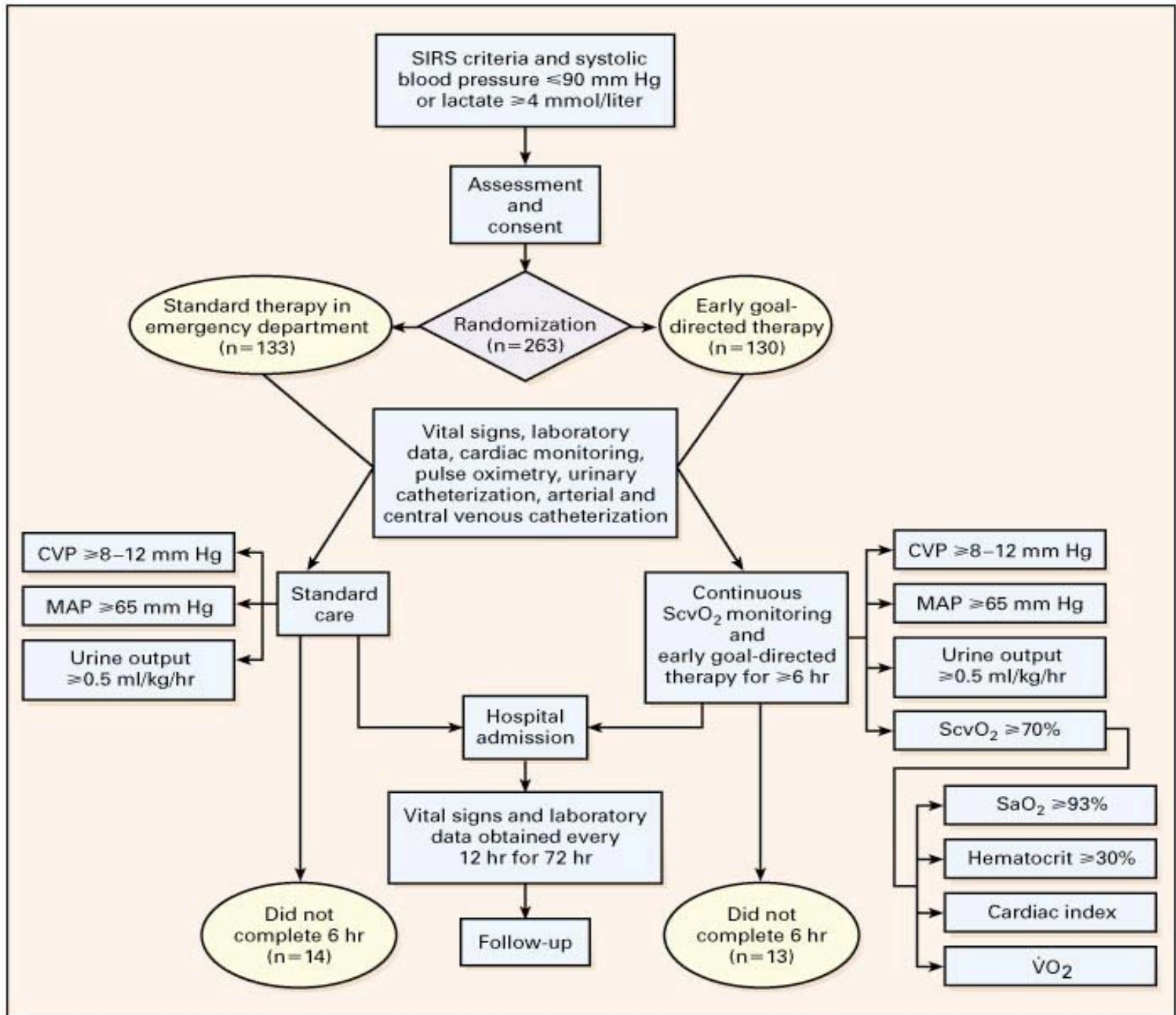


TABLE 3. KAPLAN-MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38-0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21-1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36-0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42-1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39-0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46-0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan-Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

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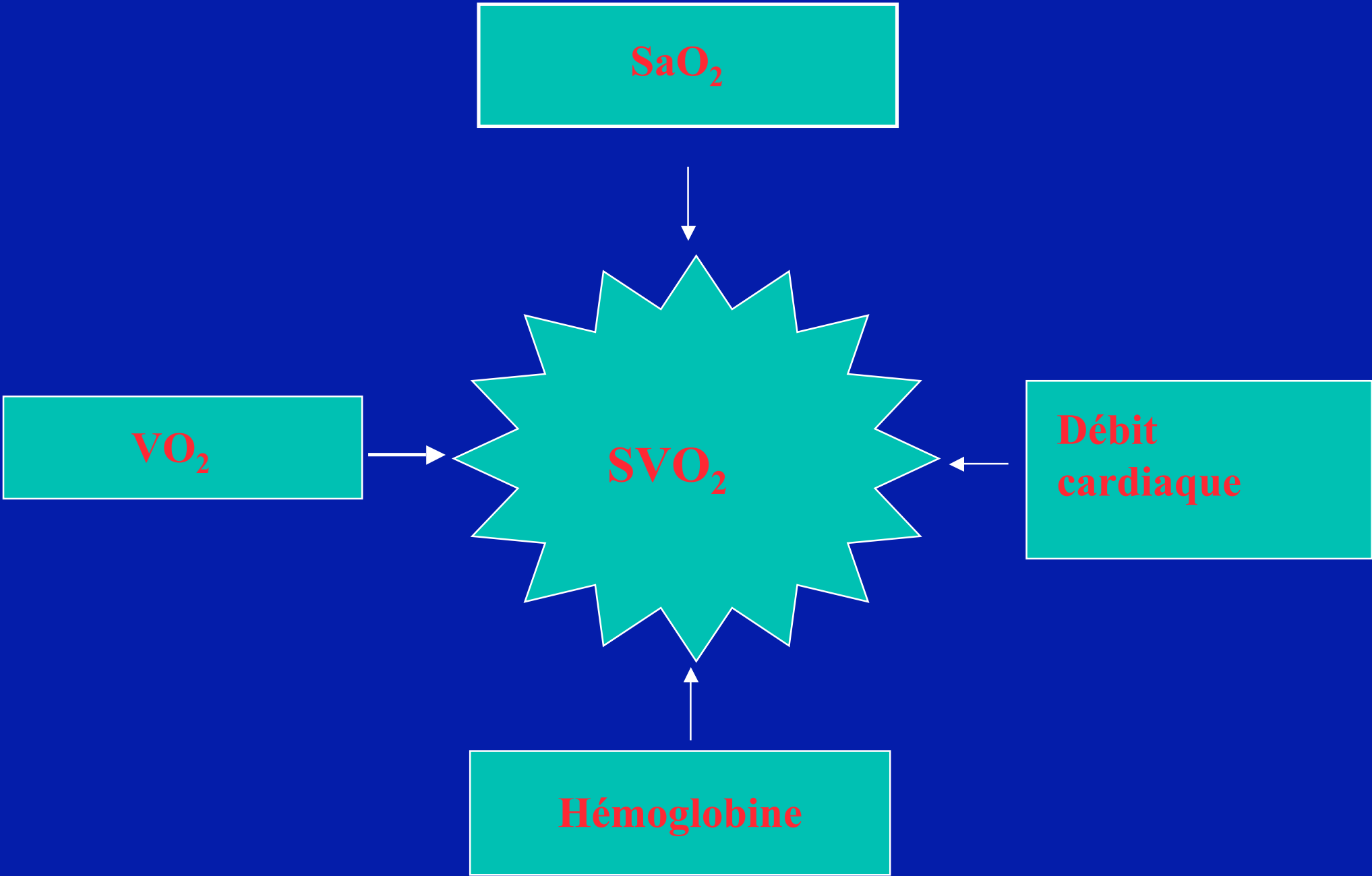
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†Percentages were calculated by the Kaplan-Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

TABLE 4. TREATMENTS ADMINISTERED. *

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0-6	7-72	0-72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01



Les questions

- PVC
- ScVO₂
- Transposition du système d'urgence au système français
- Conditions de l'implémentation

Expansion volémique et vasopresseurs

- Cristalloïdes ou colloïdes : 60 ml/kg ou plus (grade C)
- Dopamine ou norepinephrine en première intention (grade D)
 - ◆ De préférence à la fin de l'expansion volémique
 - ◆ Pas de dopamine à faible « doses »
 - ◆ Cathéter artériel
- Vasopressine en cas de choc hyperkinétique réfractaire (grade E)
- En cas de bas débit cardiaque, utiliser la dobutamine (grade E)



clinical investigations in critical care

Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?*

Claude Martin, M.D., F.C.C.P.; Laurent Papazian, M.D.;
Gilles Perrin, M.D.; Pierre Saux, M.D.; and François Gouin, M.D.

32 patients randomized to: either dopamine (until 25 $\mu\text{g}/\text{kg}/\text{min}$) or norepi (until 5 $\mu\text{g}/\text{kg}/\text{min}$)

Objective : to reach and maintain mean BP > 80 mmHg over 6 hours

Dopa (n=16)

Norepi (n=16)

success (n=5)

failure (n=11)

success (n=15)

failure (n=1)

10 to 25 $\mu\text{g}/\text{kg}/\text{min}$

25 $\mu\text{g}/\text{kg}/\text{min}$

1.5 \pm 1.2 $\mu\text{g}/\text{kg}/\text{min}$

5 $\mu\text{g}/\text{kg}/\text{min}$

increase in urine output
decrease in lactate

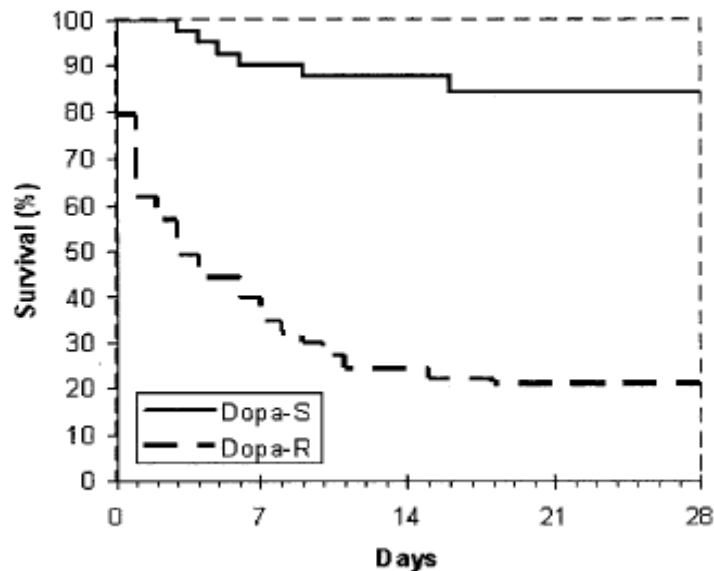
increase in urine output
decrease in lactate

10 successes with **Dopa + Norepi** (25 $\mu\text{g}/\text{kg}/\text{min}$ + 1.7 \pm 1.8 $\mu\text{g}/\text{kg}/\text{min}$)

increase in urine output
and decrease in lactate

Cardiovascular response to dopamine and early prediction of outcome in septic shock: A prospective multiple-center study*

Bruno Levy, MD, PhD; Benjamin Dusang, MD; Djillali Annane, MD, PhD; Sebastien Gibot, MD; Pierre-Edouard Bollaert, MD, PhD; and the College Interregional Des Réanimateurs Du Nord-Est



	Mortalité à J ₂₈
Population globale	53,64 %
Groupe Dopamine-sensible (40%)	15,91 %
Groupe Dopamine-résistant (60 %)	78,79 %

Crit Care Med 2005 Vol. 33, No. 10

Question 3 :

Quelle est la place des médicaments inotropes positifs et vasoactifs ?

Traitement vasoconstricteur

Les médicaments vasoconstricteurs doivent être utilisés si le remplissage vasculaire ne permet pas d'obtenir une PAM > 65 mmHg (grade B). L'utilisation précoce de ces agents est recommandée car elle permet de limiter la survenue des défaillances viscérales (grade E).

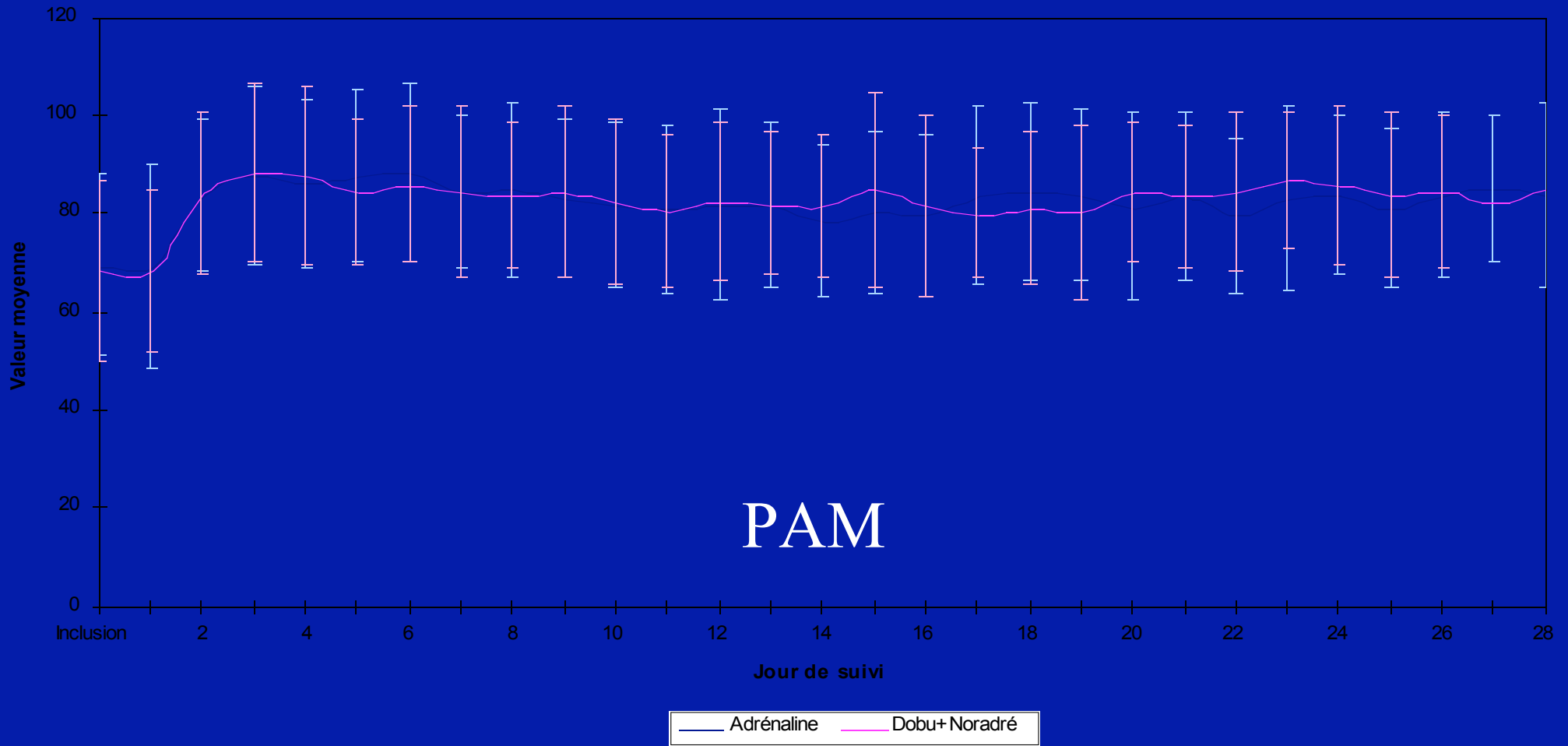
La noradrénaline étant la plus puissante des amines vasoconstrictrices, elle doit être utilisée en première intention (grade E).

La vasopressine (0,01 à 0,04 U/min) ou la terlipressine (bolus de 1 à 2 mg) peut être utilisée dans les chocs réfractaires (grade E).

ETUDE CATS

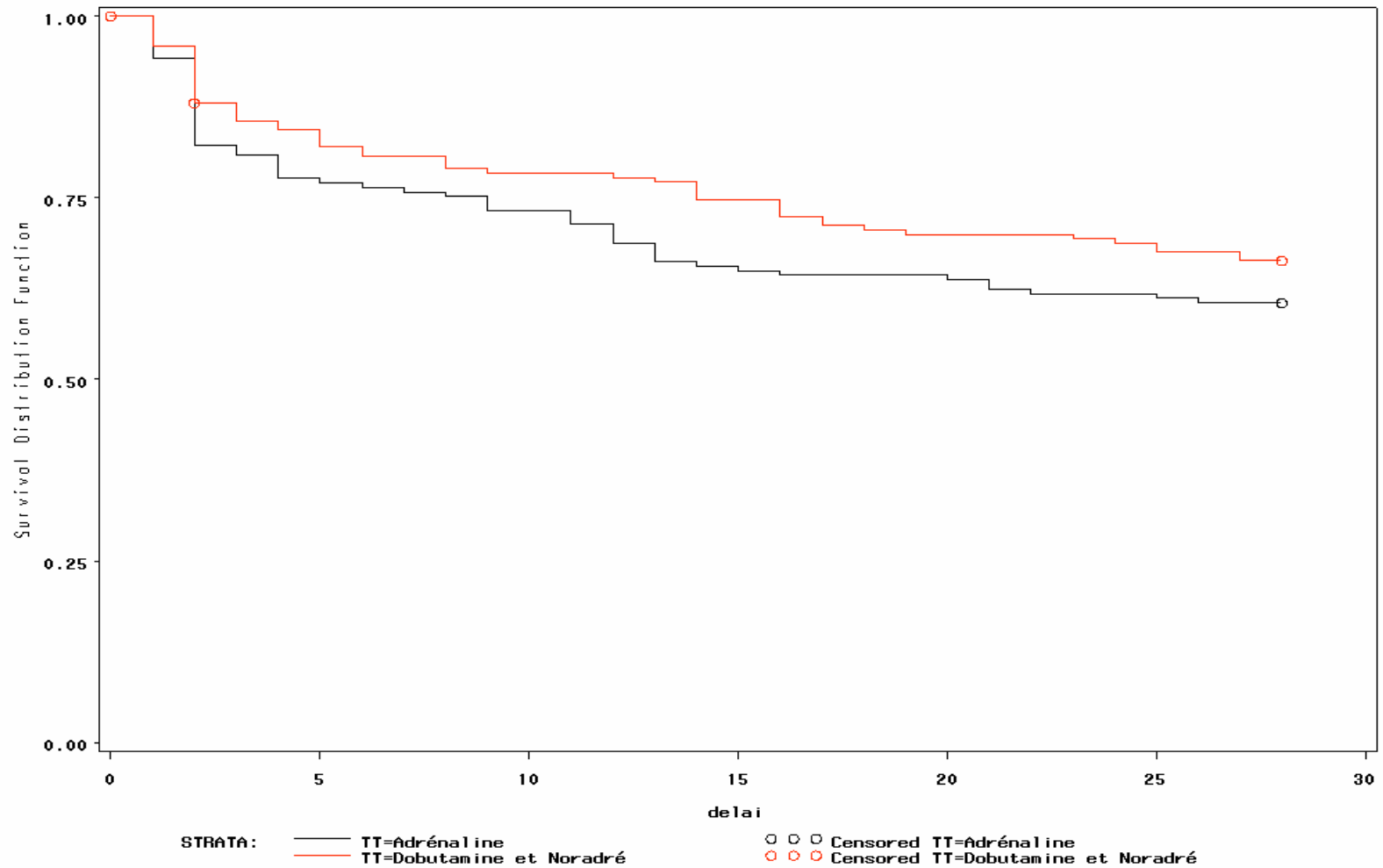
Adrénaline versus Noradrénaline + Dobutamine
pour le traitement du choc septique

SUIVI HEMODYNAMIQUE



SURVIE

Etude CATS — Sorties du 20JUN05



Thérapeutiques nouvelles

■ Corticoïdes

- ◆ Pas de fortes doses (grade A)
- ◆ HSHC : 300mg/24 h pour les patients sous catécholamines (grade C) avec ou sans test à l'ACTH et avec ou sans fludrocortisone.

■ Protéine C activée (Xigris) : grade B.

- ◆ Le plus tôt possible
- ◆ 2 défaillances viscérales

Papers

Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis

Djillali Annane, Eric Bellissant, Pierre Edouard Bollaert, Josef Briegel, Didier Keh, Yizhak Kupfer

Long courses of low dose corticosteroids

Bollaert 1998	7/22	12/19		9.84	0.50 (0.25 to 1.02)
Briegel 1999	3/20	4/20		3.05	0.75 (0.19 to 2.93)
Chawla 1999	6/23	10/21		7.98	0.55 (0.24 to 1.25)
Annane 2002	82/151	91/149		69.96	0.89 (0.73 to 1.08)
Yildiz 2002	8/20	12/20		9.16	0.67 (0.35 to 1.27)
Subtotal (95% CI)	236	229		100.0	0.80 (0.67 to 0.95)

Total events: 106 (treatment), 129 (control)

Test for heterogeneity: $\chi^2=3.94$, $df=4$, $P=0.41$, $I^2=0\%$

Test for overall effect: $z=2.49$, $P=0.01$

0.01 0.1 1 10 100
Favours treatment Favours control

CORTICUS INCLUSION CRITERIA

3. Evidence of shock

- Systolic BP < 90 mmHg or >50 mmHg fall despite adequate fluid or need for pressors >1 h (dopamine $\geq 5\mu\text{g}/\text{kg}/\text{min}$ or any dose of adr, noradr, vasopressin or phenylephrine) to maintain SBP ≥ 90 mmHg
- Hypoperfusion or organ dysfunction attributable to sepsis within previous 72h including one of:
 - sustained oliguria (<0.5 ml/kg/h for >1 hr)
 - metabolic acidosis [pH <7.3 , base deficit ≥ 5 , lactate >2]
 - platelets $\leq 100,000/\text{mm}^3$
 - GCS < 14 (or acute change from baseline)

4. Informed consent

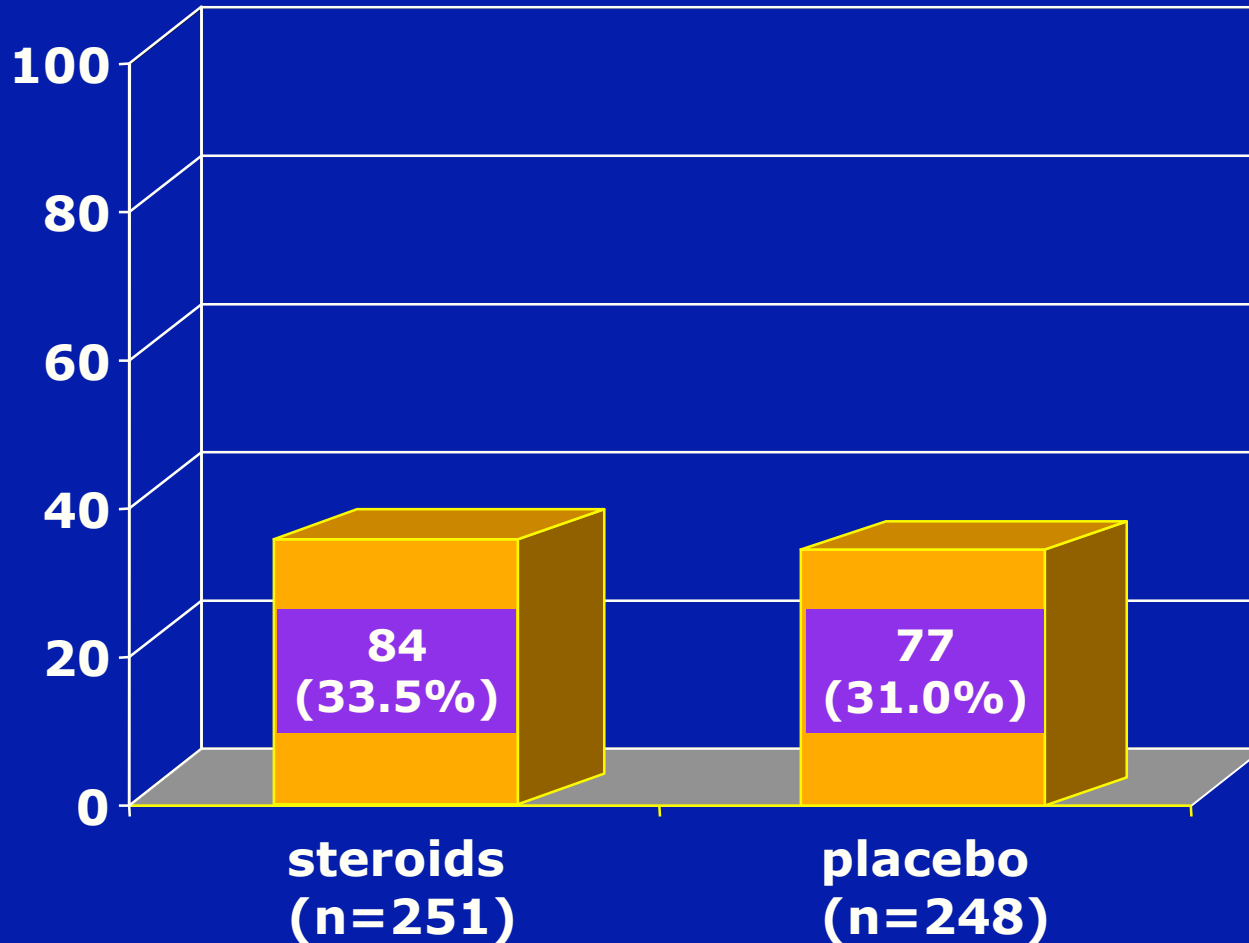
5. ACTH stimulation test

RESULTS: ACTH stimulation test

	Steroids (n=251)	Placebo (n=248)	All (n=499)
Non-responders	125 (49.8%)	108 (43.5%)	233 (46.7%)
Responders	118 (47%)	136 (54.8%)	254 (50.9%)
Unknown	8 (3.2%)	4 (1.6%)	12 (2.4%)

RESULTS: 28-day mortality - all patients

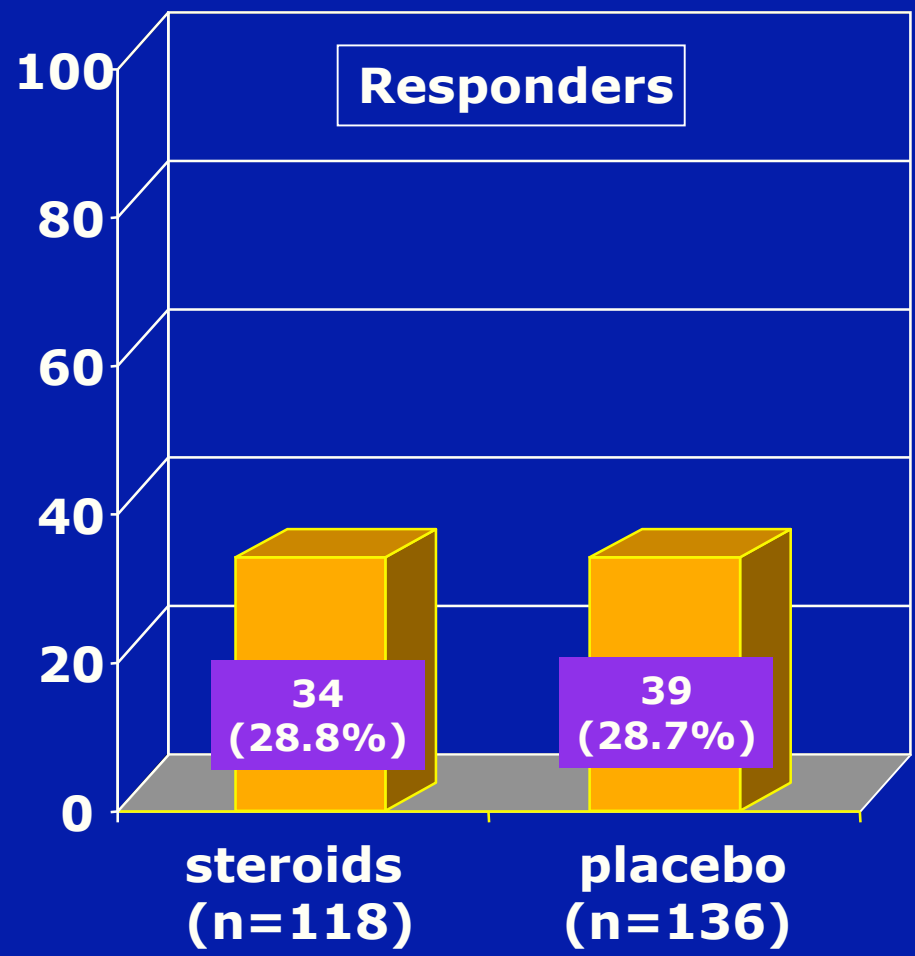
% mortality



P = 0.567

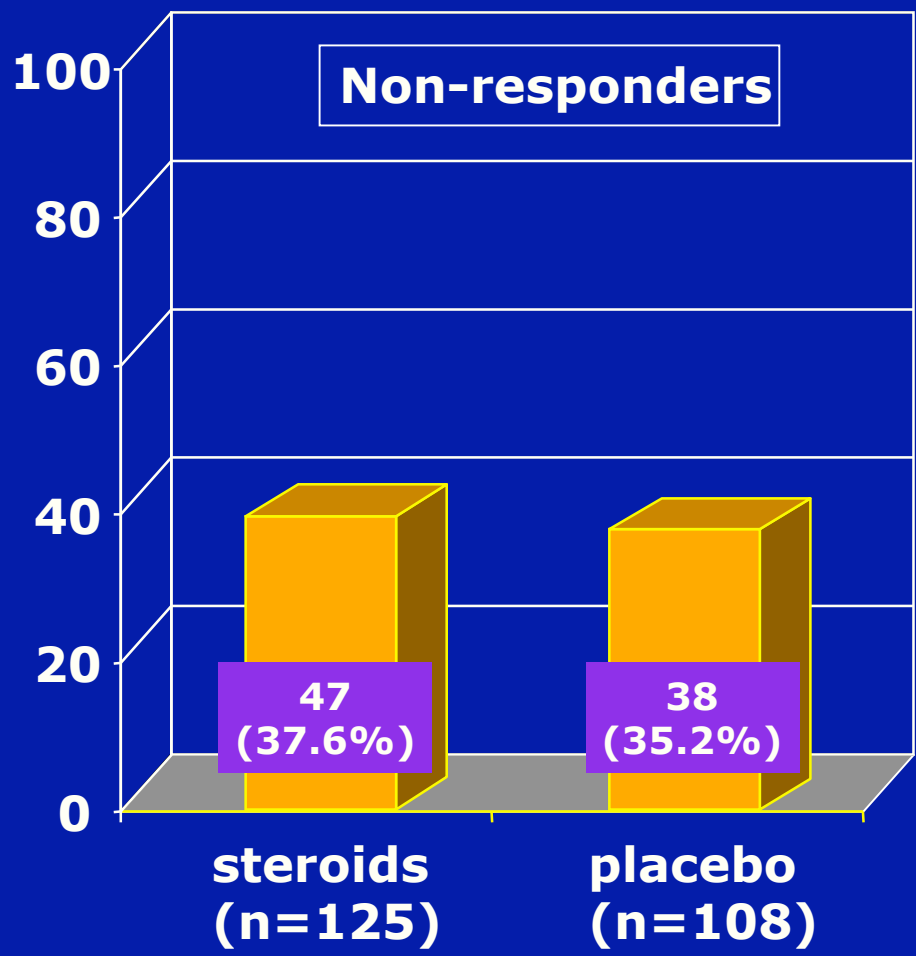
RESULTS: 28-day mortality - by response to ACTH stimulation

% mortality



P = 1.000

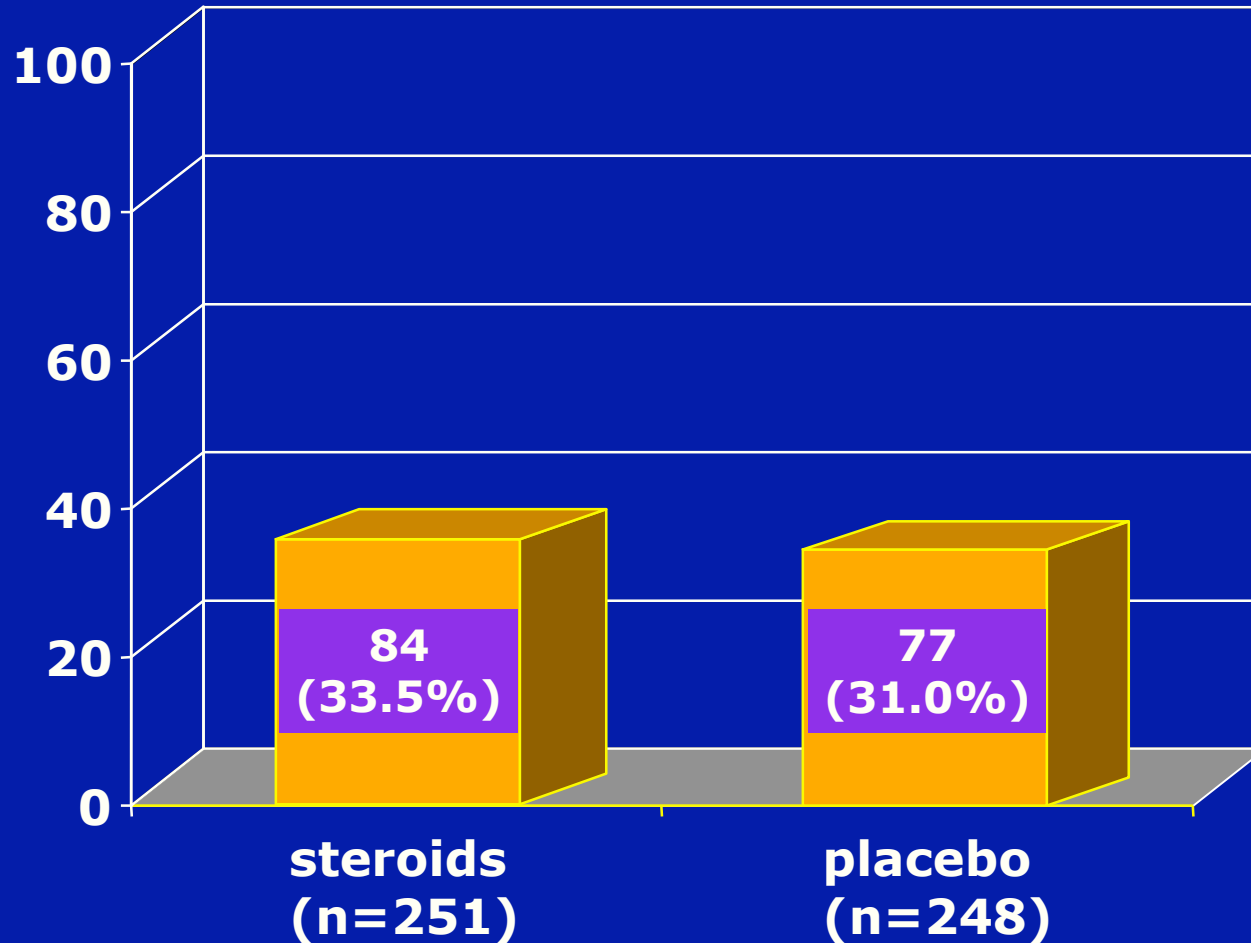
% mortality



P = 0.785

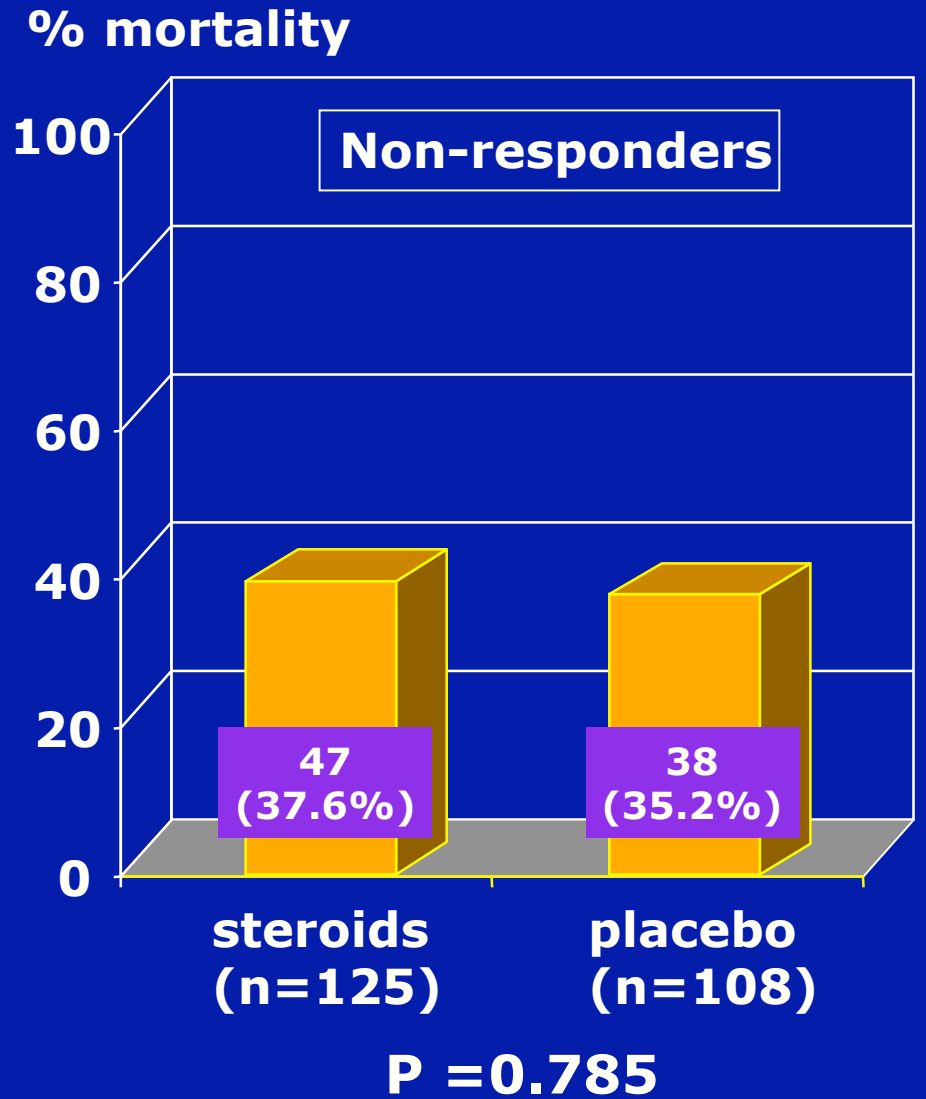
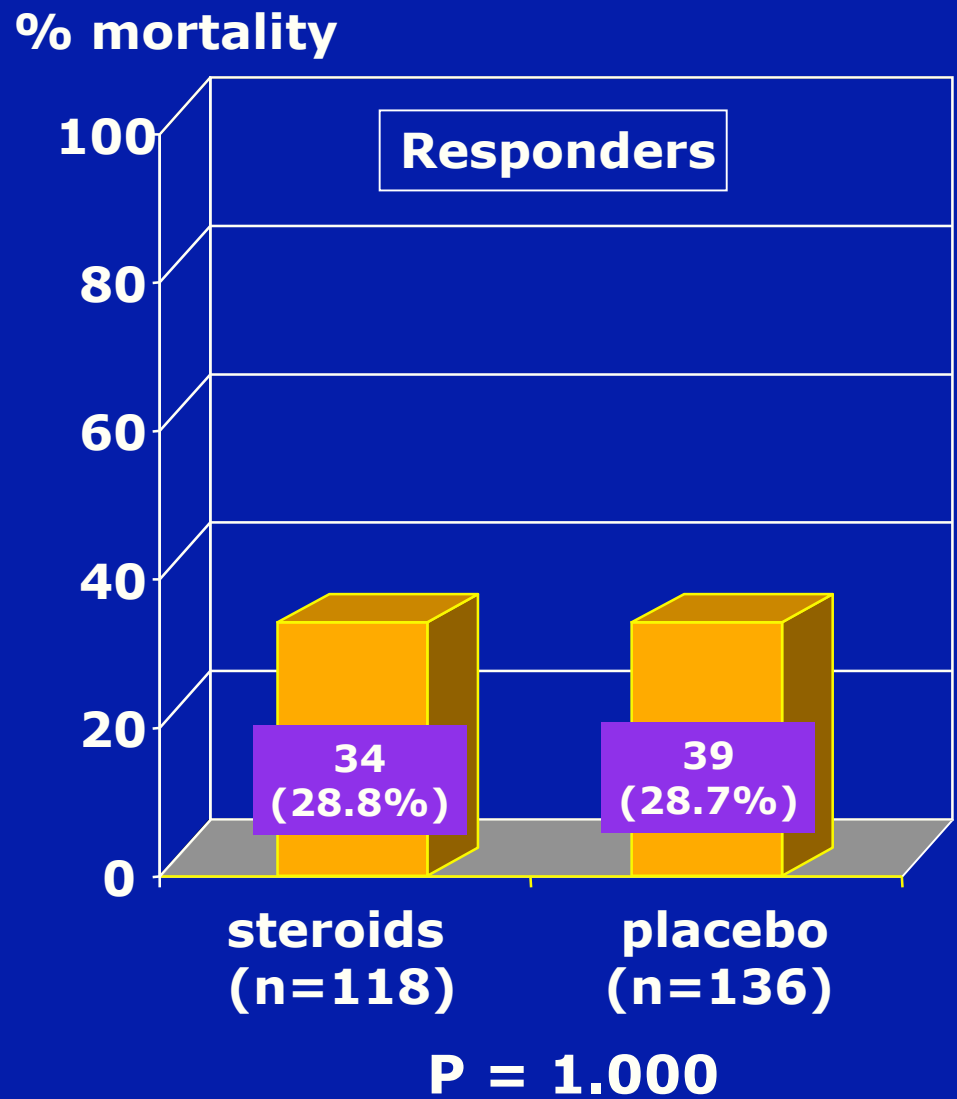
RESULTS: 28-day mortality - all patients

% mortality



P = 0.567

28-day mortality - by response to ACTH stimulation



Reversal of shock

	Steroids (n=251)	Placebo (n=248)	p
All	202 (80.5%)	185 (74.6%)	0.14
Non-responders	96 (76.8%)	76 (70.4%)	0.34
Responders	100 (84.7%)	105 (77.2%)	0.17

RESULTS: Time to reversal of shock

	Steroids (n=251)	Placebo (n=248)	P
All	3.1 (2.8-3.8)	5.7 (5.1-6.5)	0.003
Non-responders	3.7 (3.0-4.6)	6.0 (4.9-8.8)	0.046
Responders	2.8 (2.1-3.5)	5.7 (4.8-6.9)	0.003

Frequency of superinfections

	Steroids (n=234)	Placebo (n=232)
Superinfection	78 (33.3%)	61 (26.3%)
No superinfection	156 (66.7%)	171 (73.7%)

Relative risk (95% CI) = 1.27 (0.96-1.68)

Adverse events

	Steroids (n=234)	Placebo (n=232)	RR (95% CI)
Critical illness polyneuropathy	2 (1%)	4 (2%)	0.50 (0.09-2.68)
Bleeding - any site	21 (9%)	16 (7%)	1.3 (0.70-2.43)
MSOF	34 (15%)	33 (14%)	1.02 (0.66-1.59)
New sepsis	6 (3%)	2 (1%)	2.97 (0.61-14.59)
New septic shock	14 (6%)	5 (2%)	2.78 (1.02-7.58)
Repeat shock	85 (34%)	63 (25%)	1.33 (1.01-1.75)
Renal	7 (3%)	6 (3%)	1.16 (0.39-3.39)
Pulmonary	8 (3%)	13 (6%)	0.61 (0.26-1.44)
Glucose >8.3 mmol/l (day 1-7)	200 (84%)	173 (72%)	1.17 (1.06-1.28)

Corticus Harmonization Study

Central Method: Roche

	Responder Local	Nonresponder Local	Total
Responder Central	156 (37%)	22 (5%)	177 (42%)
Nonresponder Central	76 (18%)	172 (40%)	248 (58%)
	231 (55%)	194 (45%)	425

Conclusions

Hydrocortisone Rx

- **did not decrease mortality in non-responders, responders or all patients**
- **did not reverse shock in non-responders, responders or all patients**
- **did decrease the time to shock reversal in non-responders, responders and all patients**

Conclusions

Hydrocortisone Rx

- **was not associated with an increased incidence of polyneuropathy**
- **was associated with an increased incidence of superinfection and new sepsis and septic shock**

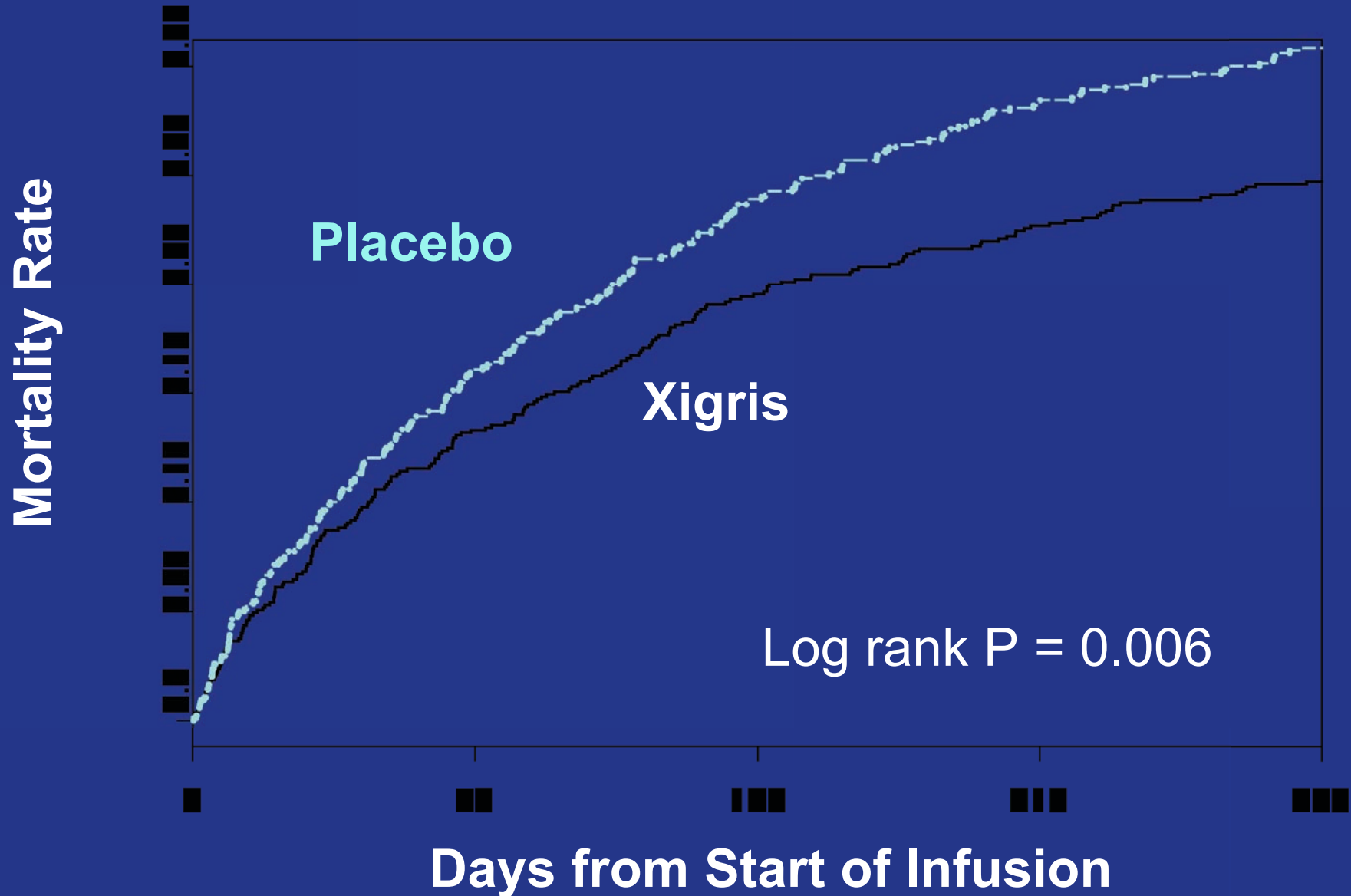
Conclusions

- **The short corticotropin test does not appear useful for guiding steroid therapy**
- **The gain achieved by earlier shock reversal in patients receiving hydrocortisone was counterbalanced by later superinfections and new sepsis and septic shock**

STUDY DIFFERENCES

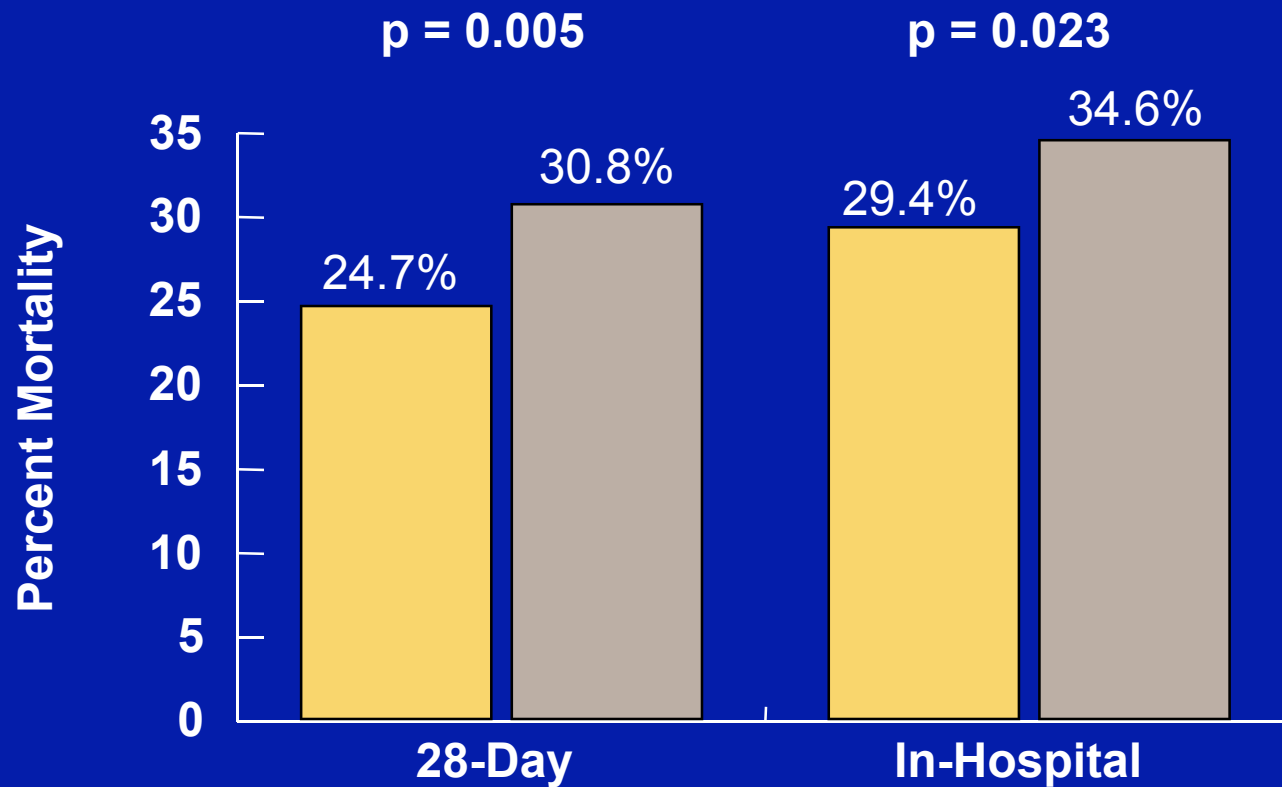
	<u>Annane</u>	<u>Corticus</u>
Entry window	8 hours	72 hours
SBP < 90 mmHg	> 1 hour	< 1 hour
Treatment	Fludrocortisone	None
Practice/Guidelines	None	Steroids used
SAPS II	59 ± 21	49 ± 17

PROWESS: Improved Survival with Xigris

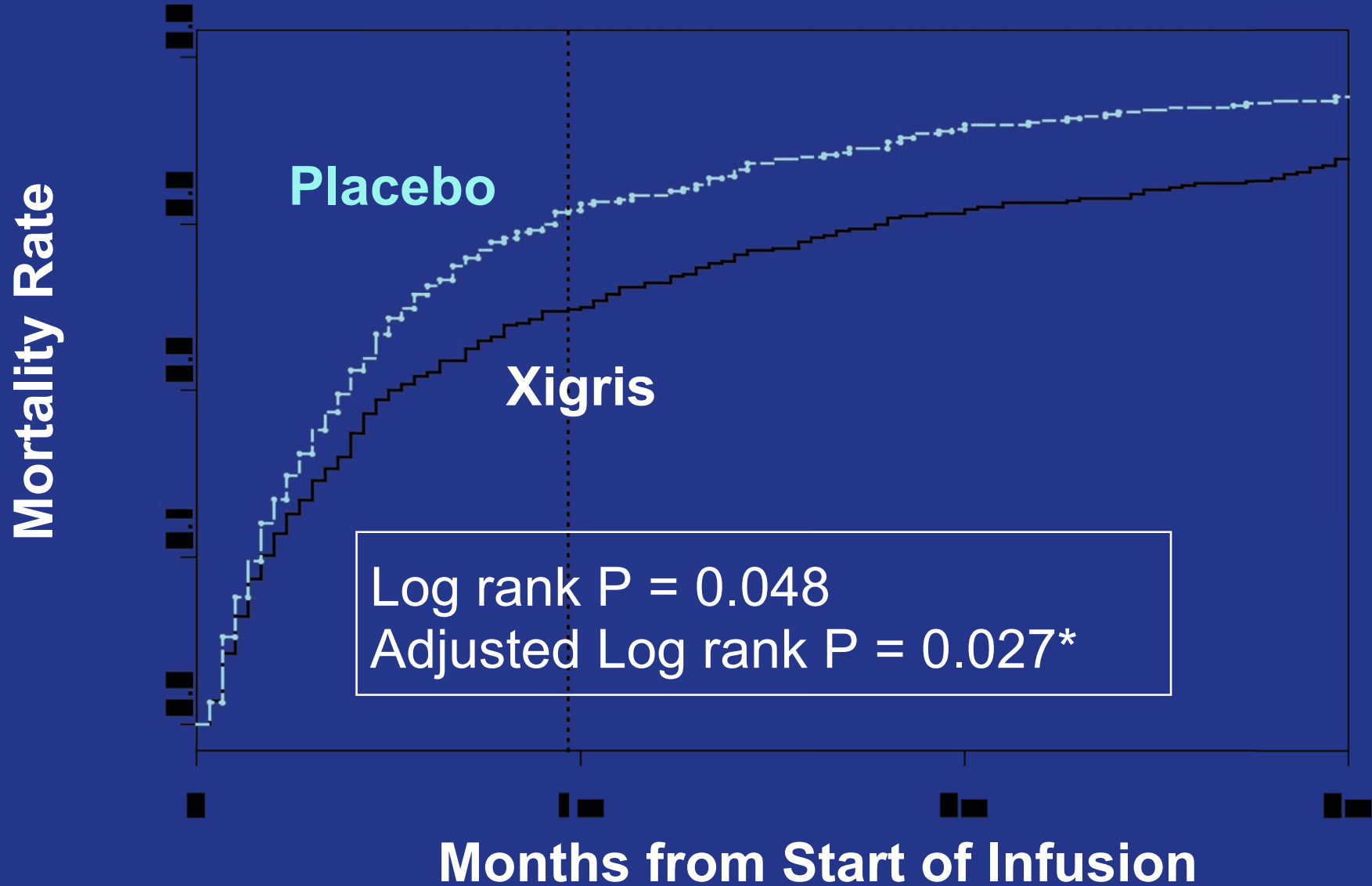


EVBI: Improved In-hospital Mortality (All Patients)

 Drotrecogin Alfa (Activated)
 Placebo

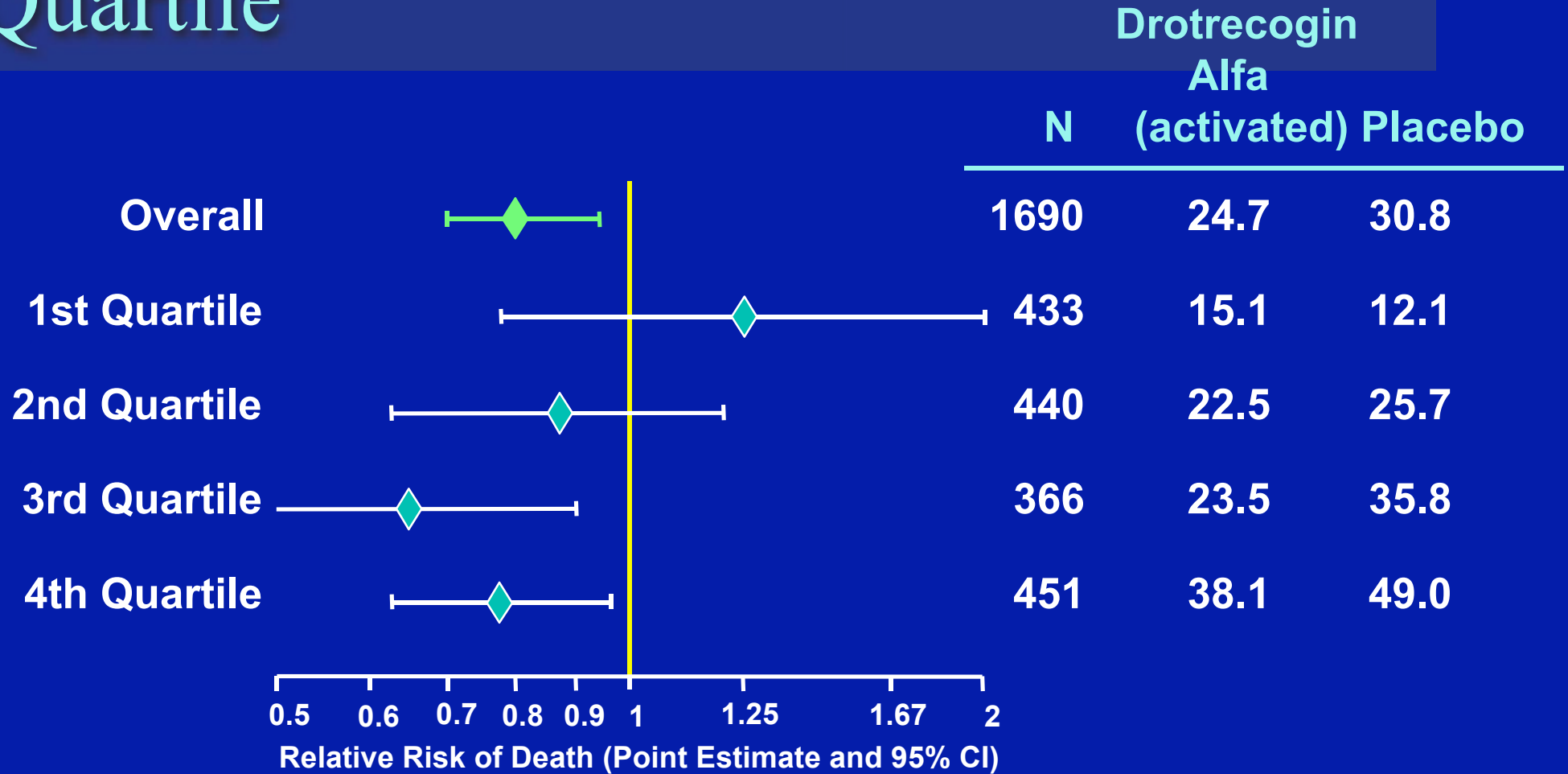


EVBI: Xigris Significantly Improves Survival over First 3 months (All Patients)



* Accounting for other predictors of 90 day outcome

PROWESS: Mortality by APACHE II Quartile



PROWESS: Bleeding Events

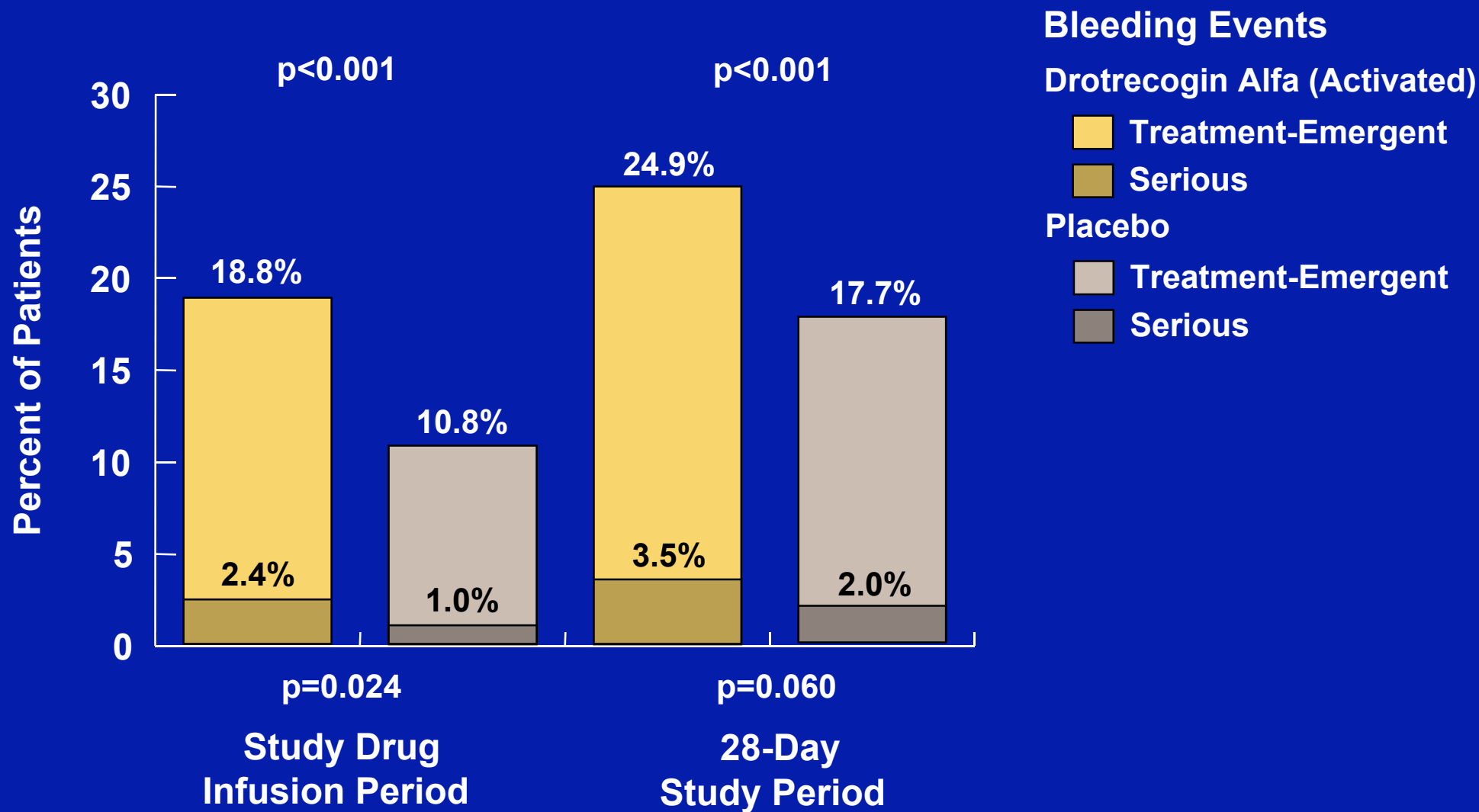


Table 5
Subgroups by APACHE II score and treatment effect in PROWESS

Population	Death in group, <i>n</i> (%)		Absolute risk reduction	RR (95% CI)
	Drotrecogin	Placebo		
APACHE II quartiles				
1st (3–19)	33/218 (15.1)	26/215 (12.1)	–3.0	1.25 (0.27–2.02)
2nd (20–24)	49/218 (22.5)	57/222 (25.7)	3.2	0.88 (0.63–1.22)
3rd (25–29)	48/204 (23.5)	58/162 (35.8)	12.3	0.66 (0.48–0.91)
4th (30–53)	80/210 (38.1)	118/241 (49.0)	10.9	0.78 (0.63–0.96)
APACHE II halves				
1st/2nd quartiles	82/436 (18.8)	83/437 (19.0)	0.2	0.99 (0.75–1.30)
3rd/4th quartiles	128/414 (30.9)	176/403 (43.7)	12.8	0.71 (0.59–0.85)

RR, relative risk; 95% CI, 95% confidence interval.

Subgroups by number of organ failures and response to treatment in PROWESS

Population	Death in group, <i>n</i> (%)		Absolute risk reduction	RR (95% CI)
	Drotrecogin	Placebo		
Number of organ dysfunctions				
1	42/216 (19.4)	43/203 (21.2)	1.8	0.92 (0.63–1.34)
2	56/270 (20.7)	71/274 (25.9)	5.3	0.80 (0.59–1.08)
3	56/214 (26.2)	75/217 (34.6)	8.4	0.76 (0.57–1.02)
≥4	56/150 (37.3)	70/146 (47.9)	10.6	0.78 (0.60–1.02)
Single vs. multiple organ dysfunction				
1	42/216 (19.4)	43/203 (21.2)	1.8	0.92 (0.63–1.34)
≥2	168/634 (26.5)	216/637 (33.9)	7.4	0.78 (0.66–0.93)

RR, relative risk; 95% CI, 95% confidence interval.

Les questions

■ Qui traiter

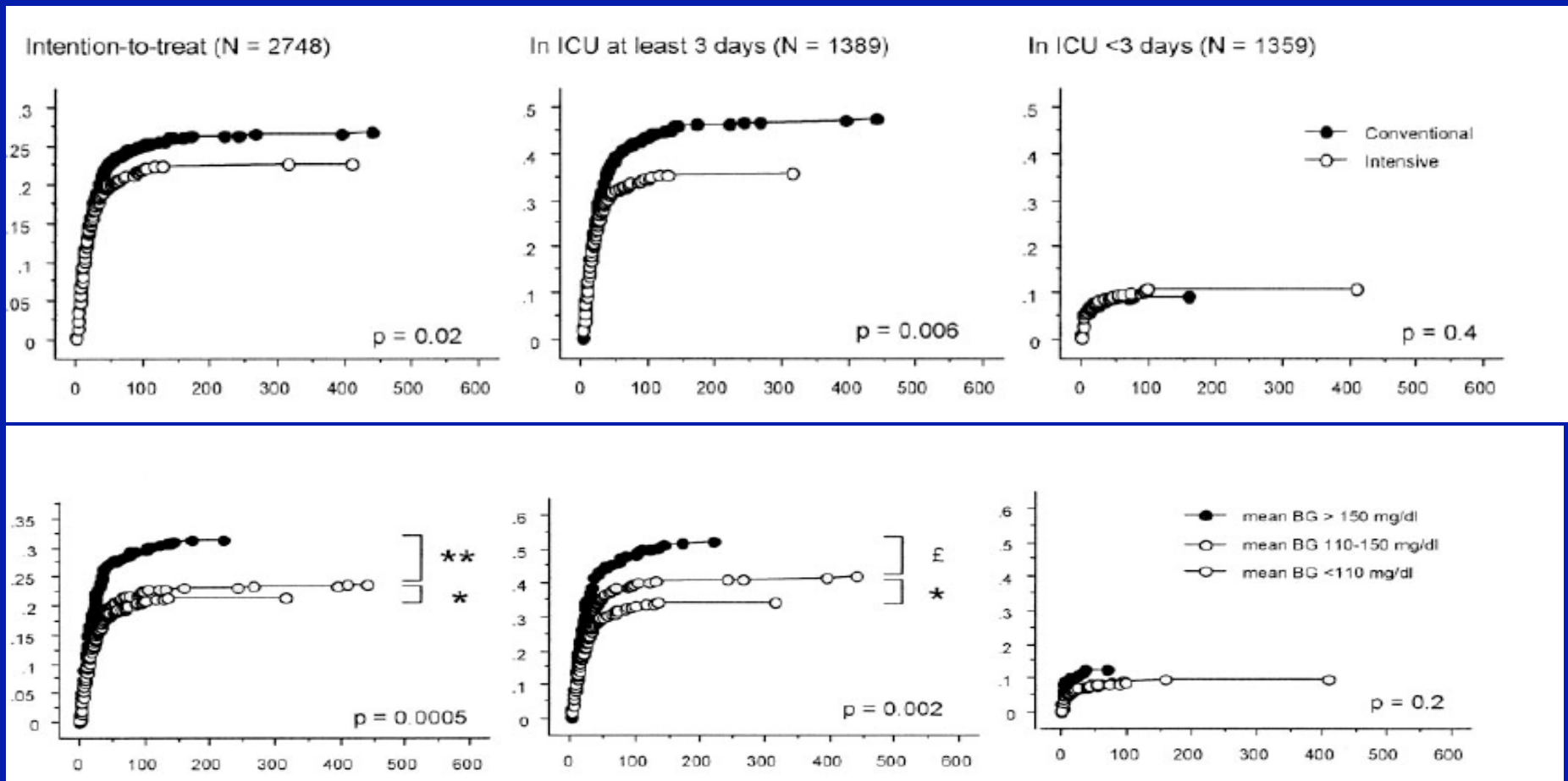
- ◆ Défaillance cardiovasculaire obligatoire
- ◆ Caractère évolutif du sepsis : résistance aux catécholamines ?
- ◆ Absence de CI
- ◆ Mortalité prédite élevée

Contrôle glycémique

- Maintenir la glycémie en dessous de 1.5 g/l
 - ◆ Insulinothérapie SE
 - ◆ Apport de dextrose 5 ou 10%
 - ◆ Nutrition entérale préférée
 - ◆ Contrôles glycémiques toutes les $\frac{1}{2}$ heures en phase aiguë puis toutes les quatre heures dès stabilisation
- Grade D

Original Article

Intensive Insulin Therapy in Mixed Medical/Surgical Intensive Care Units Benefit Versus Harm



Epuration extra-rénale

- Pas d'indication en cas d'absence d'insuffisance rénale
- Pas d'indication d'HFVVC à très haut débit
- Egalité hémodialyse intermittente –HFVVC (grade B)
 - ◆ Préférence pour l'HFVVC en cas d'instabilité hémodynamique

Notre protocole

■ H0 :

- ◆ Pose VVC, KT artériel et sonde à ScVO2 ou Swann-Ganz à débit continu
- ◆ Intubation si nécessaire
- ◆ Expansion volémique monitorée par les variations de pression artérielle pulsée et/ou échocardiographie et/ou SCVO2 et/ou Picco
- ◆ Catécholamines pour PAM entre 65 et 70 mmHg

Maniement des catécholamines

- En première intention : noradrénaline, immédiatement si PAM < 40 mmHg
- Vasopressine/terlipressine si échec et patient hyperkinétique
- Objectifs : PAM entre 65 et 70 mmHg, SCVO₂ > 70 % ou SVO₂ > 75 %

Prise en charge

- Antibiothérapie : délai maximal de une heure
- Test au synactène et HSHC en fonction du profil : à rediscuter, pas d'étomidate
- H6 à H12 : considérer le Xigris si le patient à deux défaillances viscérales, sous catécholamines et en l'absence de CI
- Glycémie < 1.5 g/l