JOURNÉES DE PRINTEMPS DE LA SFNEP
STRASBOURG 2010 - ENSPS d'Illkirch

Y a-t-il une place en Réa pour une nutrition pharmacologique ?

17 juin 2010

25 min

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CHUV

Nutrition pharmacologique - concept

Nutriments avec propriétés « spécifiques bénéfiques » identifiables

Dose pharmacologique >>> nutritionnelles dans le but d'obtenir des effets spécifiques

Administration en sus de la nutrition de base

Pharmaconutriments - candidats

Nutriment	Pourquoi?
Glutamine	AA conditionnellement essentiel
	essentiel pour cellules à renouvellement rapide
Sélénium	antioxydant charnière
	impliqué dans immunité
Zinc	essentiel pour anabolisme et immunité
	impliquée dans défenses antioxydantes
Omega-3	propriétés modulatrices de l'inflammation
	anti arythmique
Arginine	AA impliqué dans réactivité vasculaire (NO)
	cicatrisation
Autres	

Patients candidats Réa à la pharmaconutrition

Catégorie SI	Candidat?
Infarctus – Pontage AC simples	non
Chirurgie réglée simple (ex: cholécytectomie)	non
Chirurgie majeure qui se complique	oui ?
Pancréatite sévère (Balthazar C,D,E)	oui
ARDS, choc septique	oui
Brûlés graves > 20% BSA	oui
Polytraumatisés graves	oui
Transplantation (cœur, foie, poumons)	oui

« patients inflammatoires »

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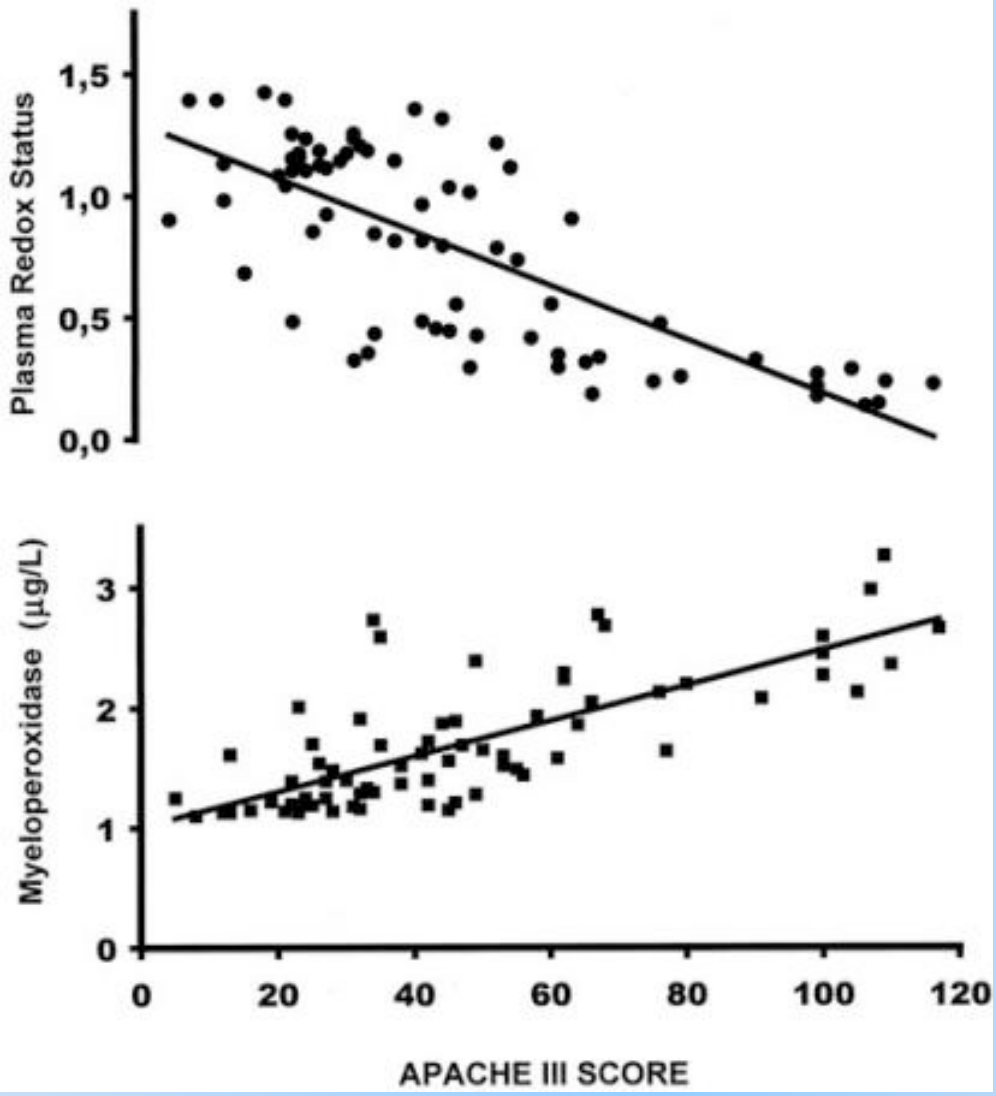
Stress oxydant et SIRS

Très fréquents et intenses en Réa

Plasma redox status relates to severity in critically ill patients

Alonso de Vega J et al, CCM 28:1812, 2000



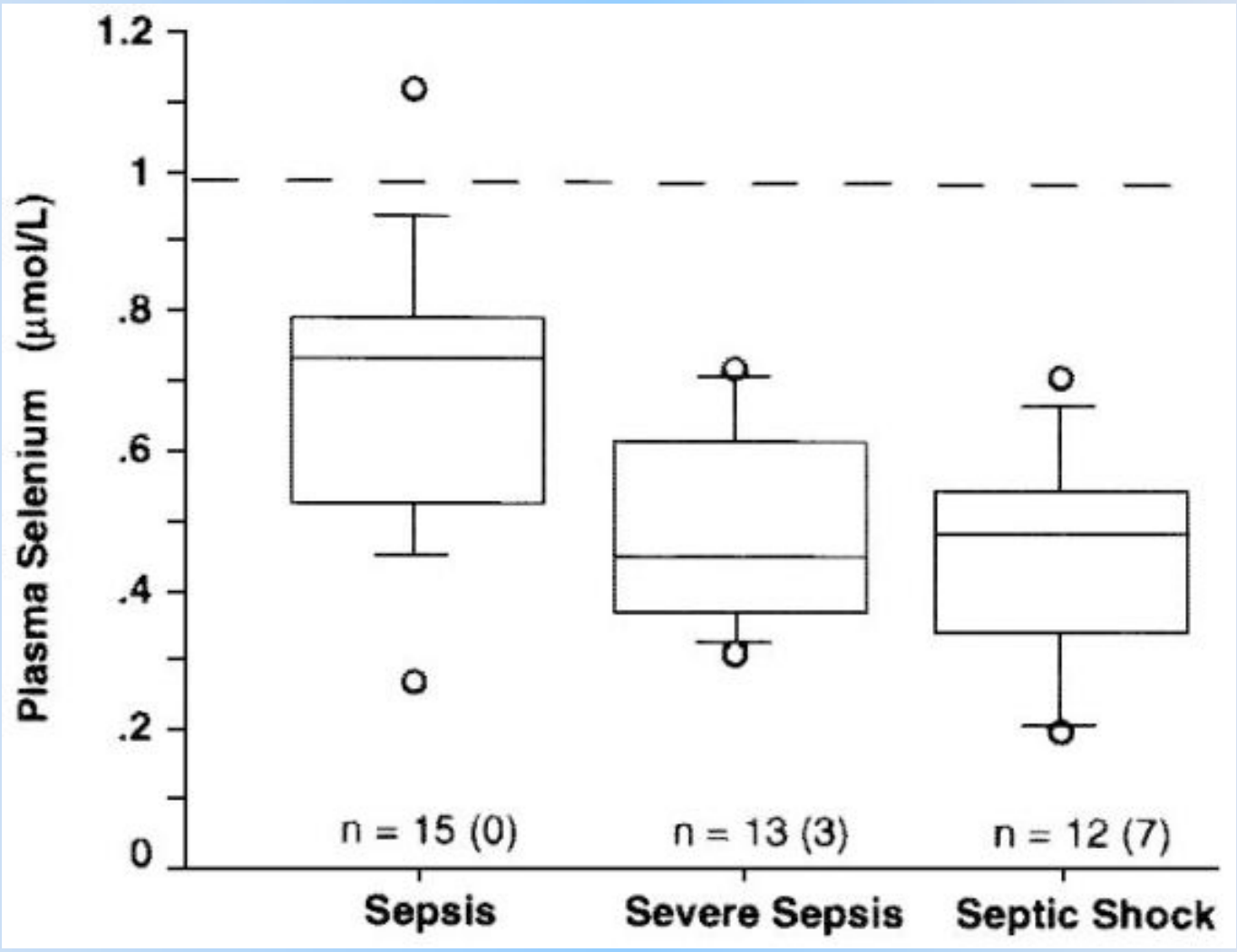
APACHE III scores and plasma redox status (r^2 = 0.56; p < .001) as defined by the ratio total antioxidant capacity (mM) / lipoperoxides (uM)

APACHE III scores and plasma myeloperoxidase concentrations (r^2 = 058; p < .001)

73 patients at admission to a mixed ICU: 8 deaths

Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients

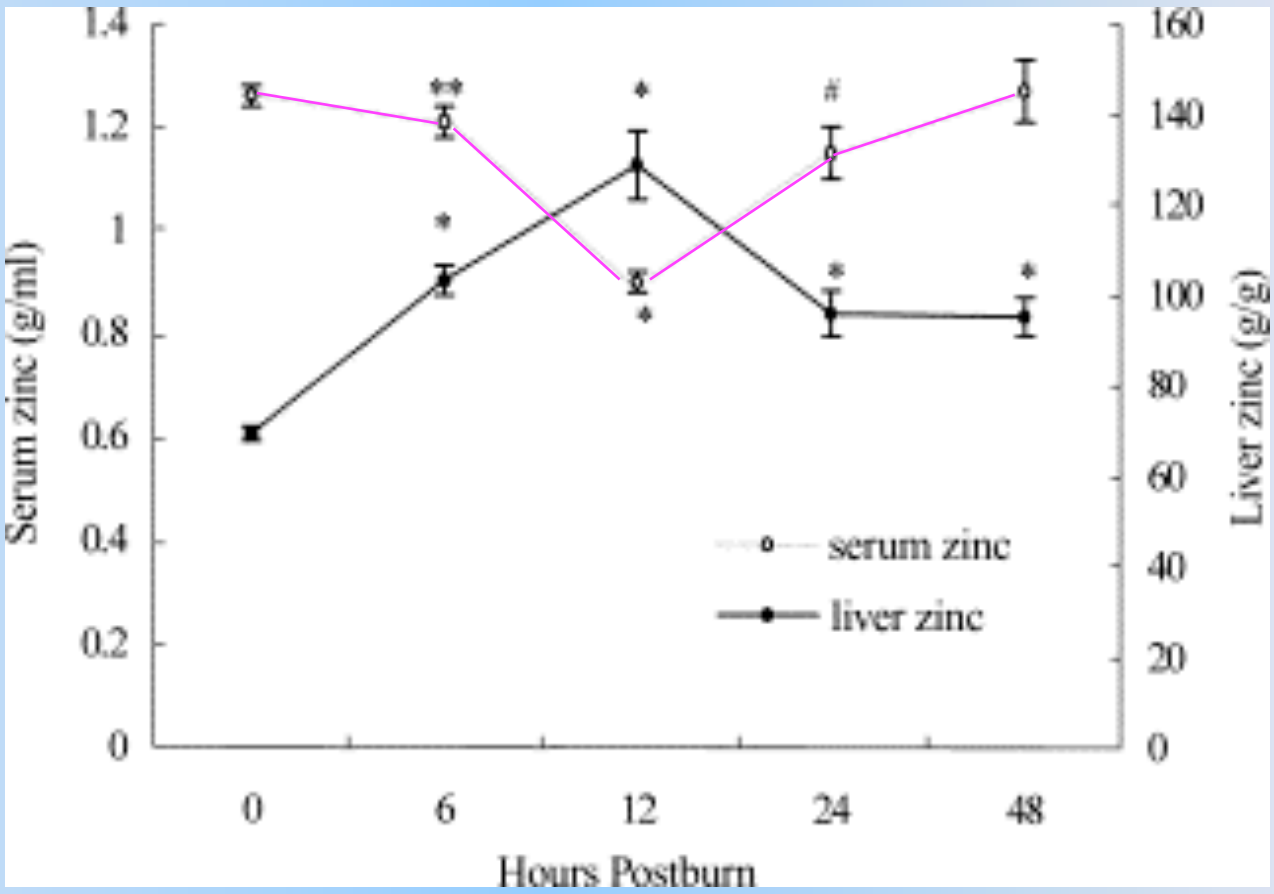
Forceville X et al, CCM 26:1536, 1998



Admission plasma [Se] related to severity of sepsis

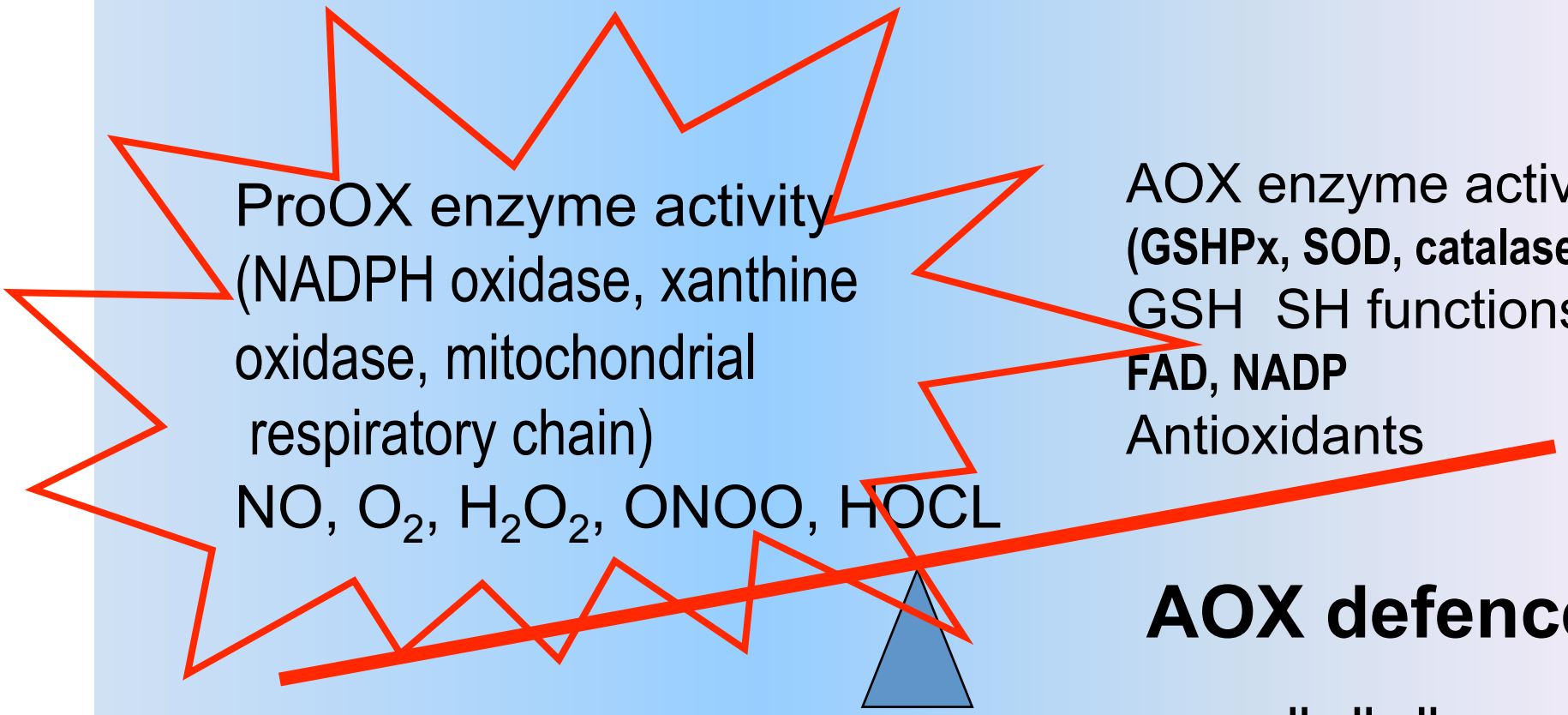
Oxidative stress and metallothionein expression - liver of rats with severe thermal injury

Ding et al Burns, 28:215, 2002



Effects of severe thermal injury on the zinc concentrations both in the serum and in the liver. mean±sem, *n*=5. $^{*}P<0.001$, $^{**}P<0.01$ and $^{\#}P<0.05$ vs. the corresponding normal control

Redox balance during critical illness



AOX defences

⇓ ⇓ ⇓

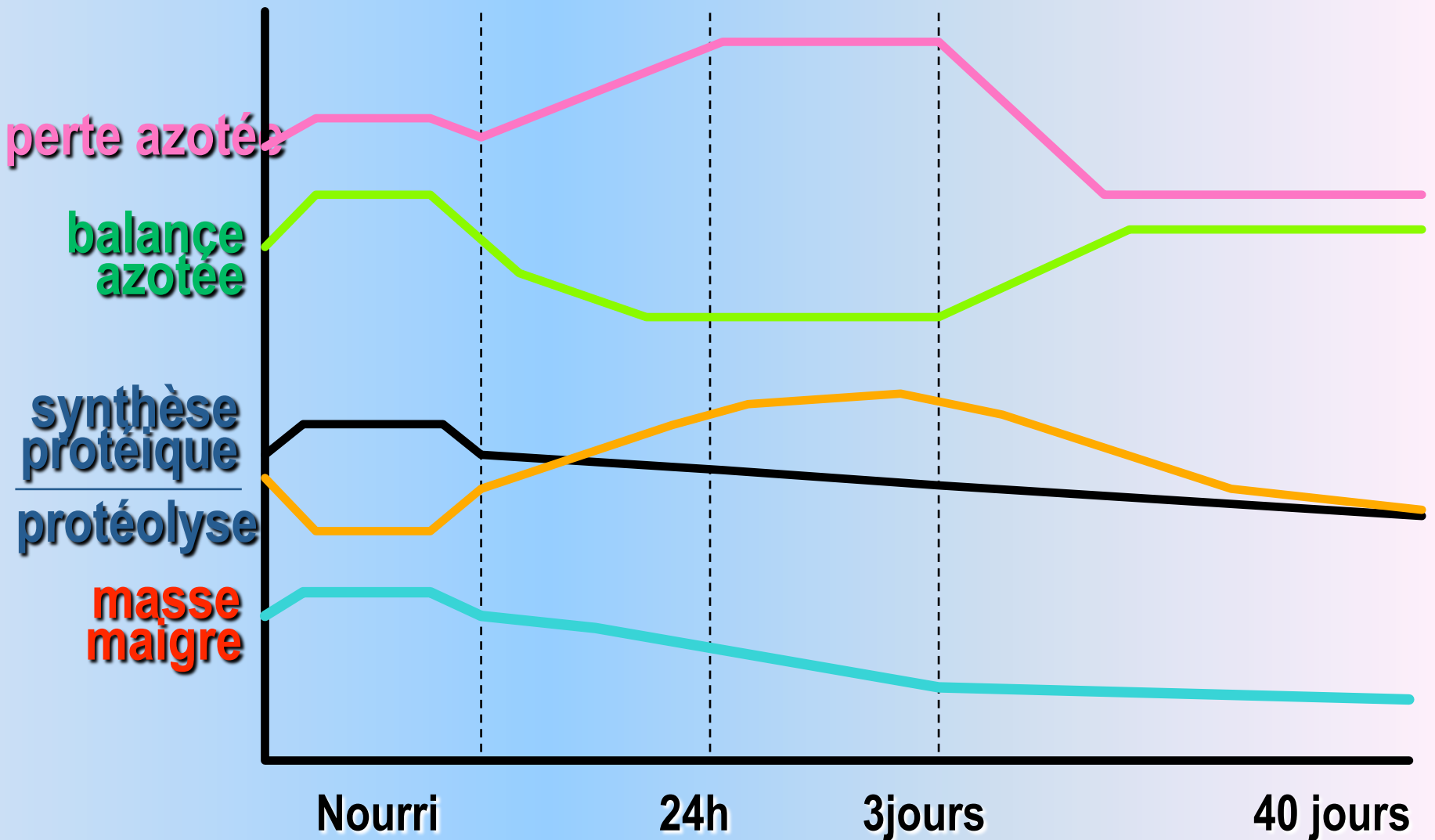
Oxidative stress

ICU patients ⇑ ⇑ ⇑

Variabilité des pathologies & des patients

Adaptation au jeûne
Métabolisme des Protéines

† Bernard Beaufrère 1998



Réponse inflammatoire
Modifications métaboliques

Hypermétabolisme très fréquent

Protéines
- mobilisation des AA tissus (glutamine)
- ↑ catabolisme et du turnover

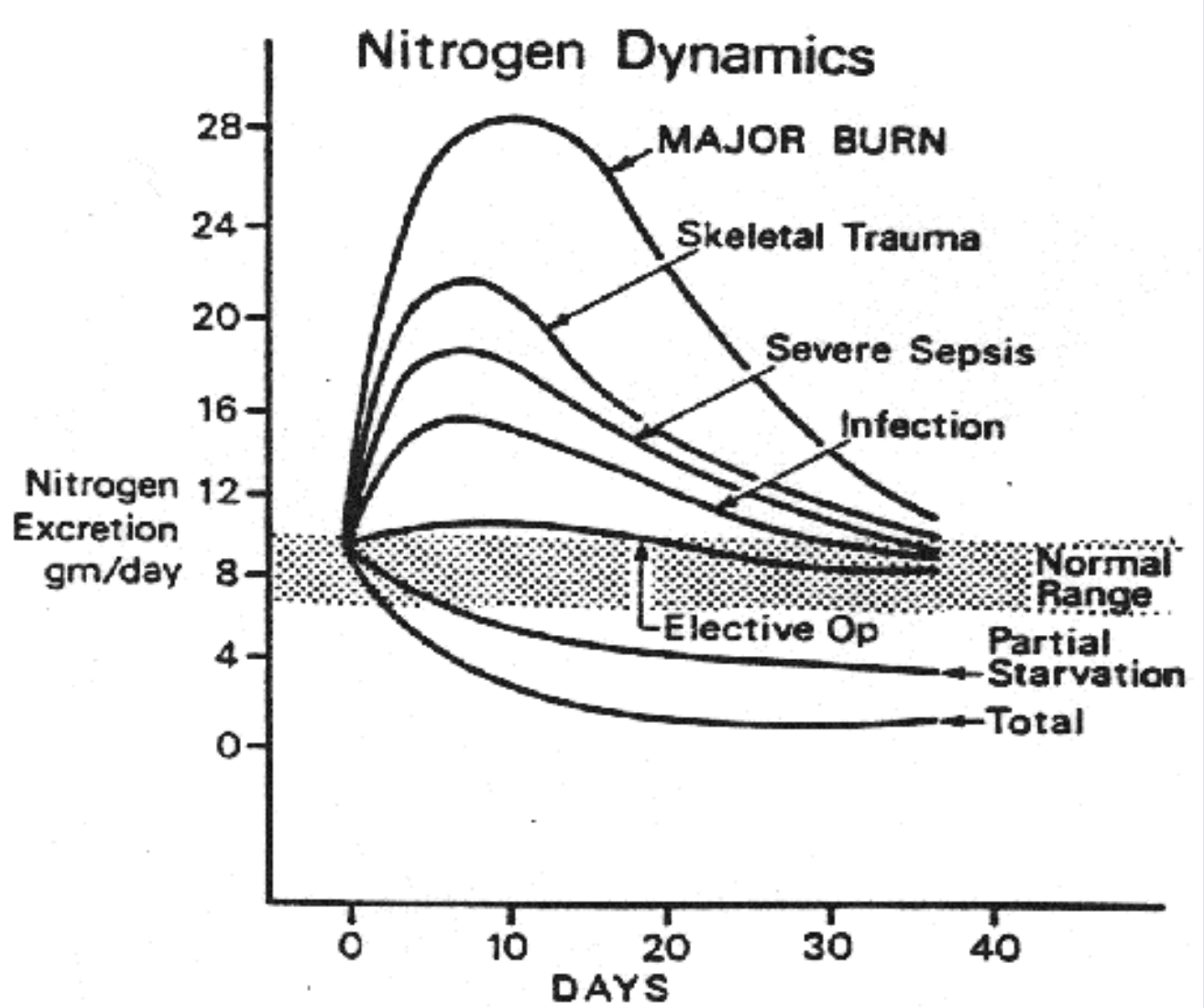
Glucose
- ↑ production endogène glucose et du turnover
- résistance à l'insuline, hyperglycémie

Graisses
- ↑ lipolyse et utilisation des lipides

Adaptation au jeune perturbée

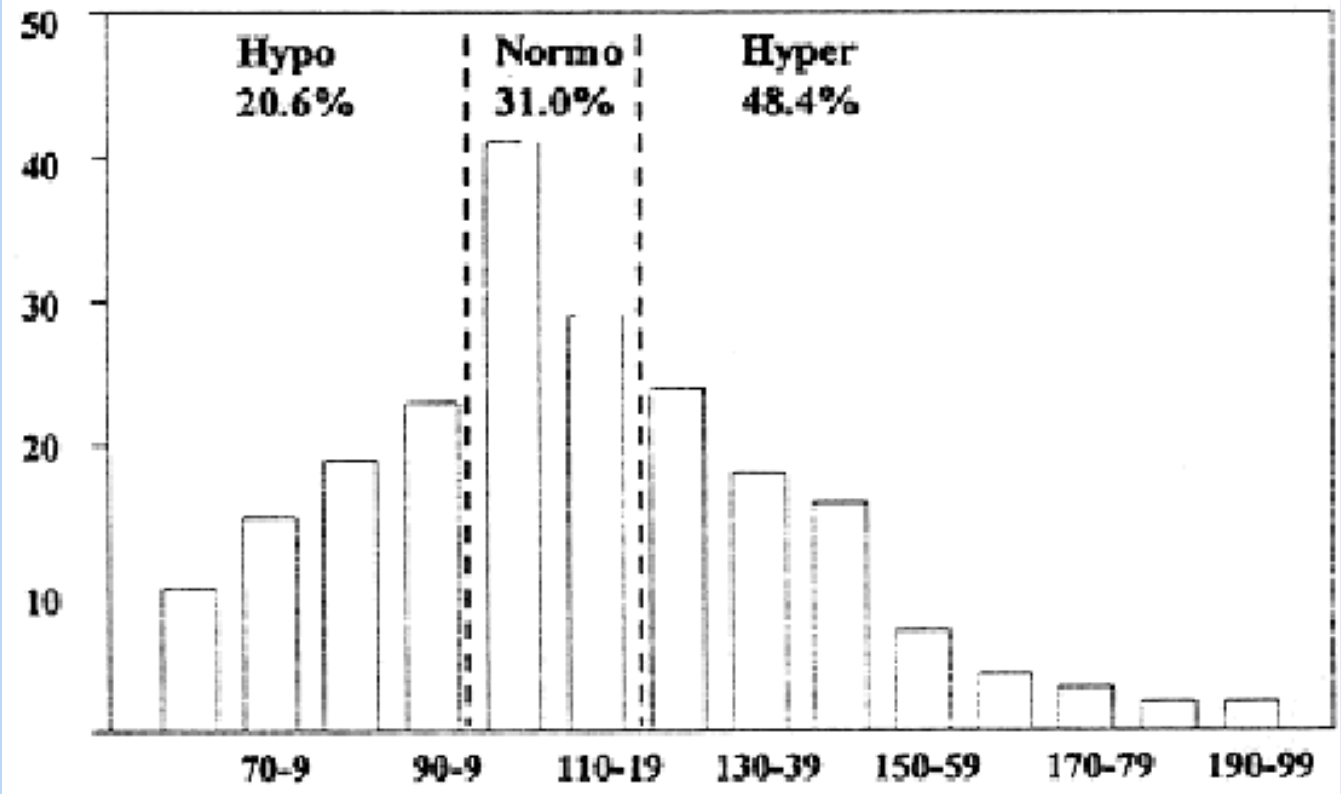
Métabolisme et Nutrition du Brûlé Grave

Catabolisme



Distribution of patients by % metabolism

McClave SA et al, JPEN 1998, 22:375



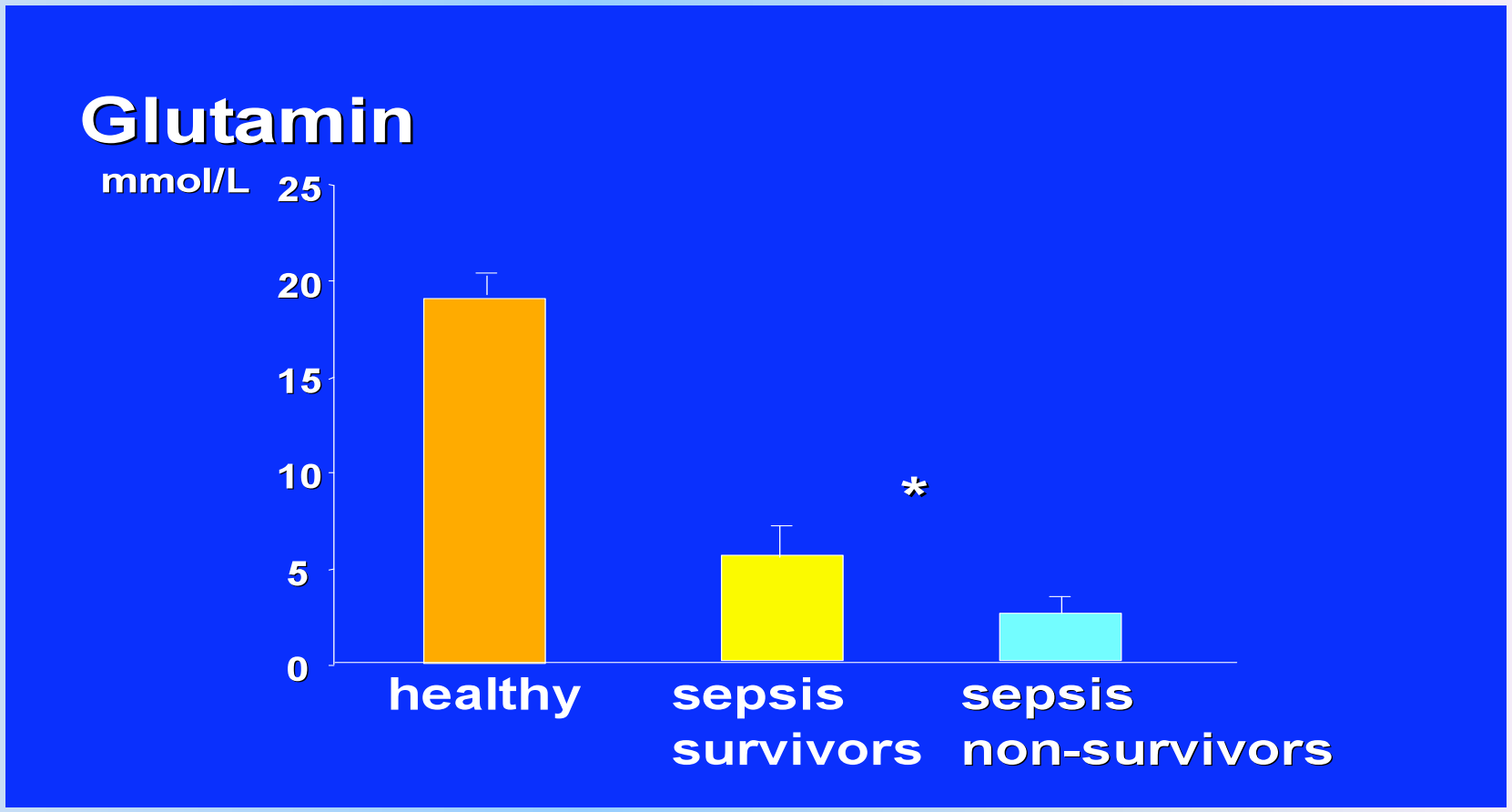
% Metabolism (MREE/HB-REE x 100)

Calorimetry in 213 patients on mechanical ventilation

Glutamine i.v.

Patients de réa sous nutrition parentérale totale

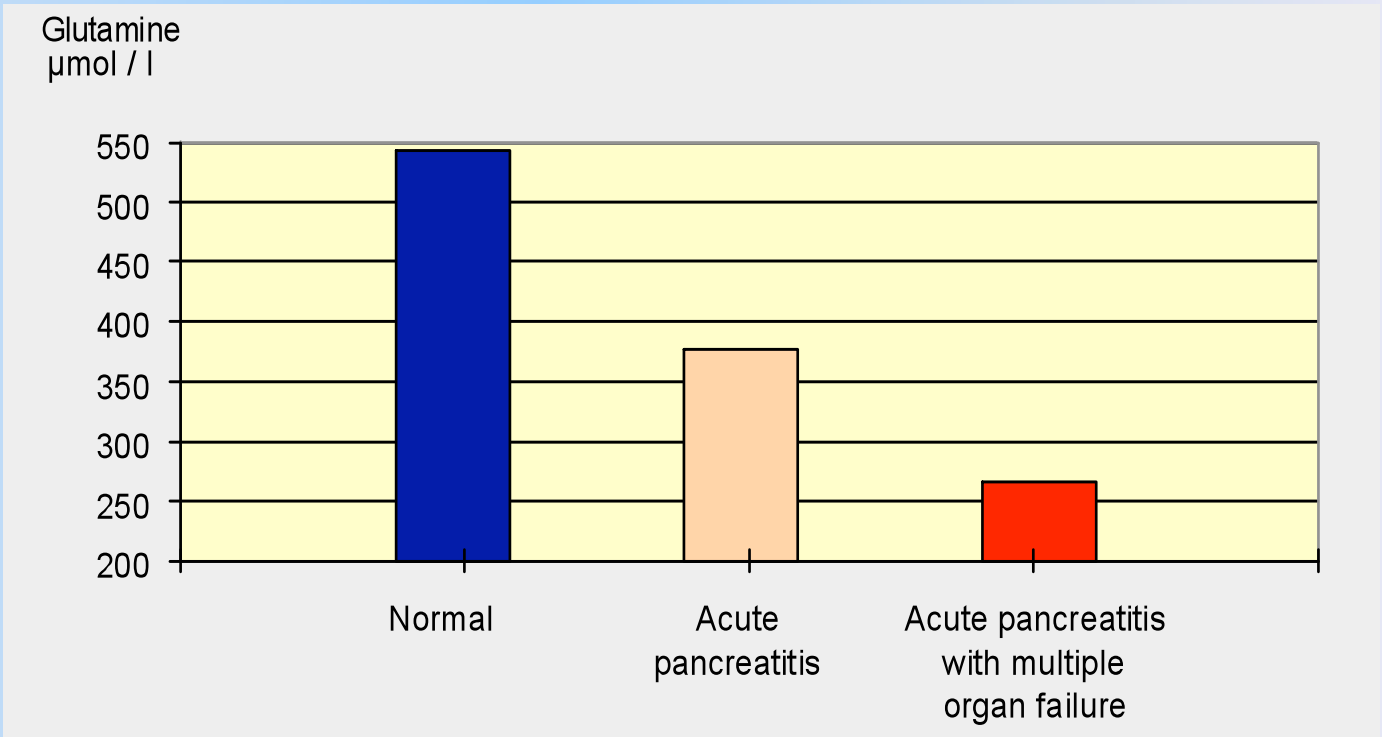
Catabolic illness → intramuscular glutamine depletion



...which is associated with increased mortality in critically ill[1]

[1] Roth E 1982

Glutamine depletion in plasma – and severity of disease[1]



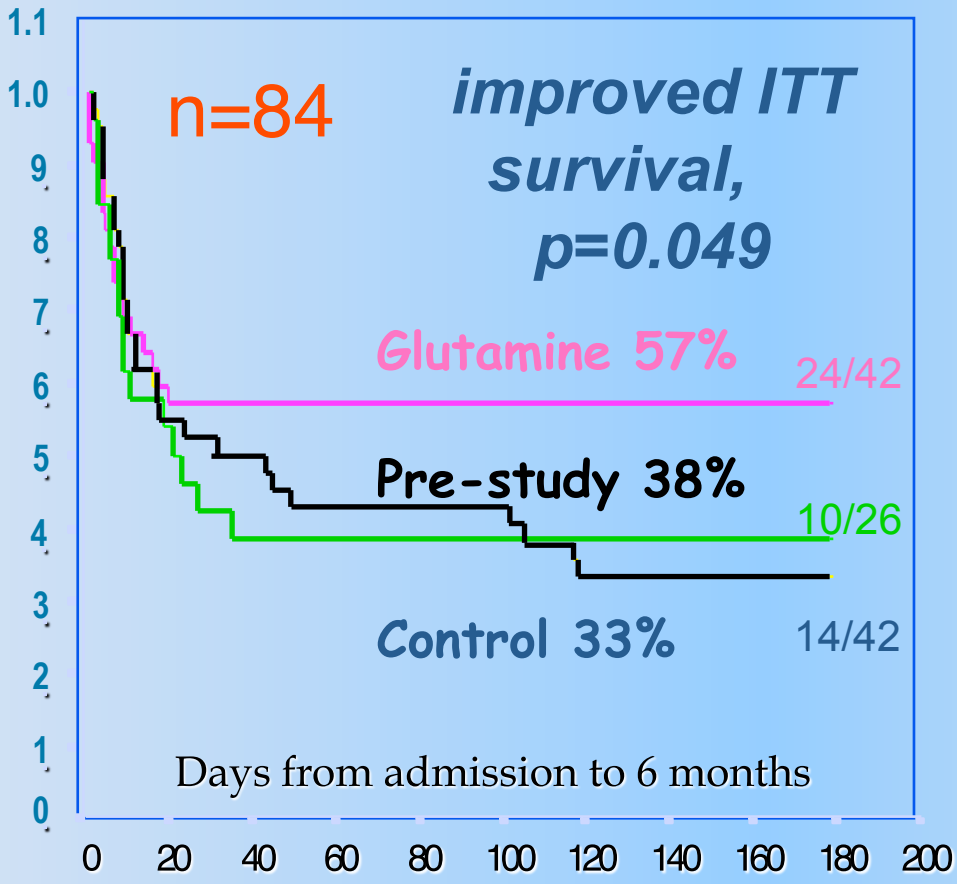
⇨ **The sicker the patient the higher the glutamine demand**

⇨ **Low plasma glutamine at admission to ICU associated with a risk of poor outcome.[2]**

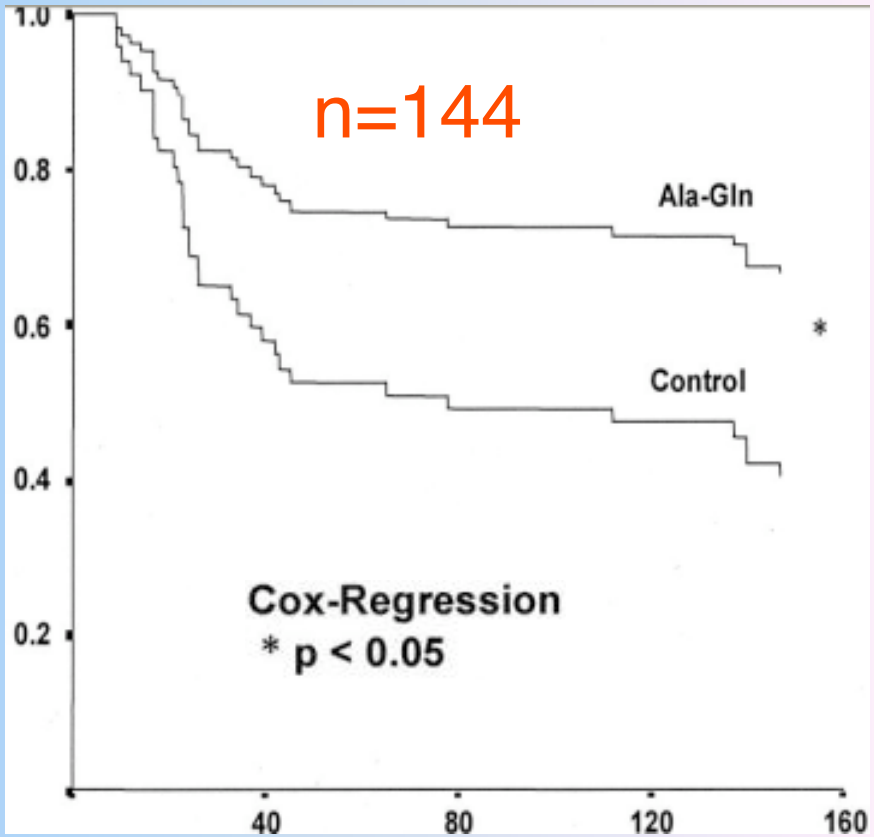
[1] **Roth** et al. 1986, [2] **Oudemans-Van Straaten** et al. 2001

Evidence of improved survival outcome with IV glutamine

Griffiths et al. Nutrition 1997; 13:295-302
Griffiths el. Nutrition 2002; 18:546-552



Goeters C et al
Crit Care Med 2002;30(9):2032-7



Alanyl-glutamine PN in ICU patients: a French double-blind multicentre study

Déchelotte P et al, Crit Care Med 2006; 34:598

TPN to 114 ICU patients

- Trauma (38), surgery (65), pancreatitis (11)

Ala-gln 0.5 g/kg/day (about 21g Gln) –v- ala-proline

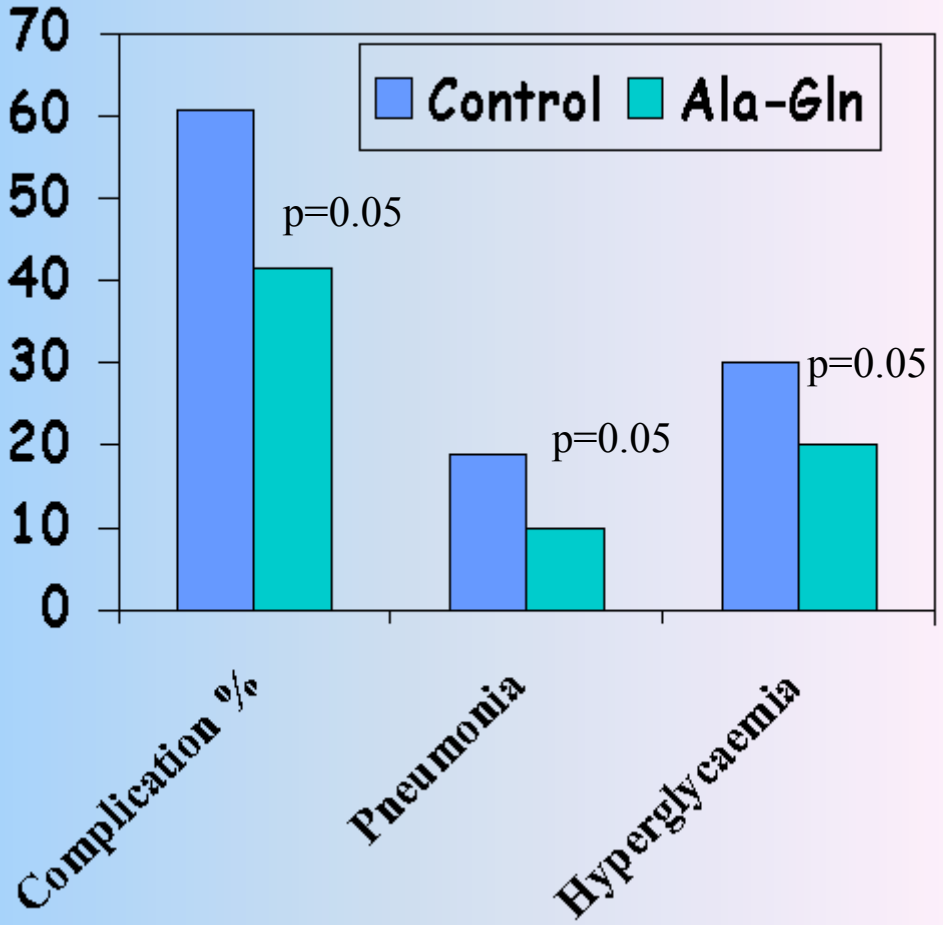
- 37.5 kcal & 1.5g AA/kg
- Median feed duration 6.8 d

Max duration 10 days

Well matched

Similar 6/12 survival

Reduced infection rate of 0.45 v 0.71 ($p<0.05$)



Glutamine

Par voie IV:

nombreuses études positives >> neutres /négatives

- Bénéfices cliniques
- Bénéficies biochimiques

Par voie digestive: c'est moins clair

nombreuses études neutres – sans effet

MAIS: aucun effet secondaire

Micronutriments antioxydants
Sélénium - Zinc
chez les patients à risque

Brûlé, polytraumatisé, choc septique, ARDS, pancréatite, TX

Zinc deficiency increases sepsis mortality
Knoell DL et al, 2009 CCM

Design: Prospective, randomized, controlled animal study.

Intervention: C57BL/6 mice randomized into 3 groups:

1) control diet,

2) zinc-deficient diet for 3 weeks,

3) zinc-deficient diet for 3 weeks followed by oral zinc supplements for 3 days (n=35 per diet).

Mice assigned to receive either CLP or sham operation (n=15 each per diet).

CLP and sham-op groups further assigned to a 7-day survival study (n=10 per ttt per diet) or were evaluated at 24 hrs (n=5 per ttt per diet) for organ damage.

Zinc deficiency increases sepsis mortality
Knoell DL et al, 2009 CCM

Results:

Sepsis mortality significantly ↑ with zinc-deficiency (90% vs. 30% in control).

Zinc-deficient animals subject to CLP had higher plasma cytokines, more severe organ injury, including ↑ oxidative tissue damage and cell death (lungs and spleen).

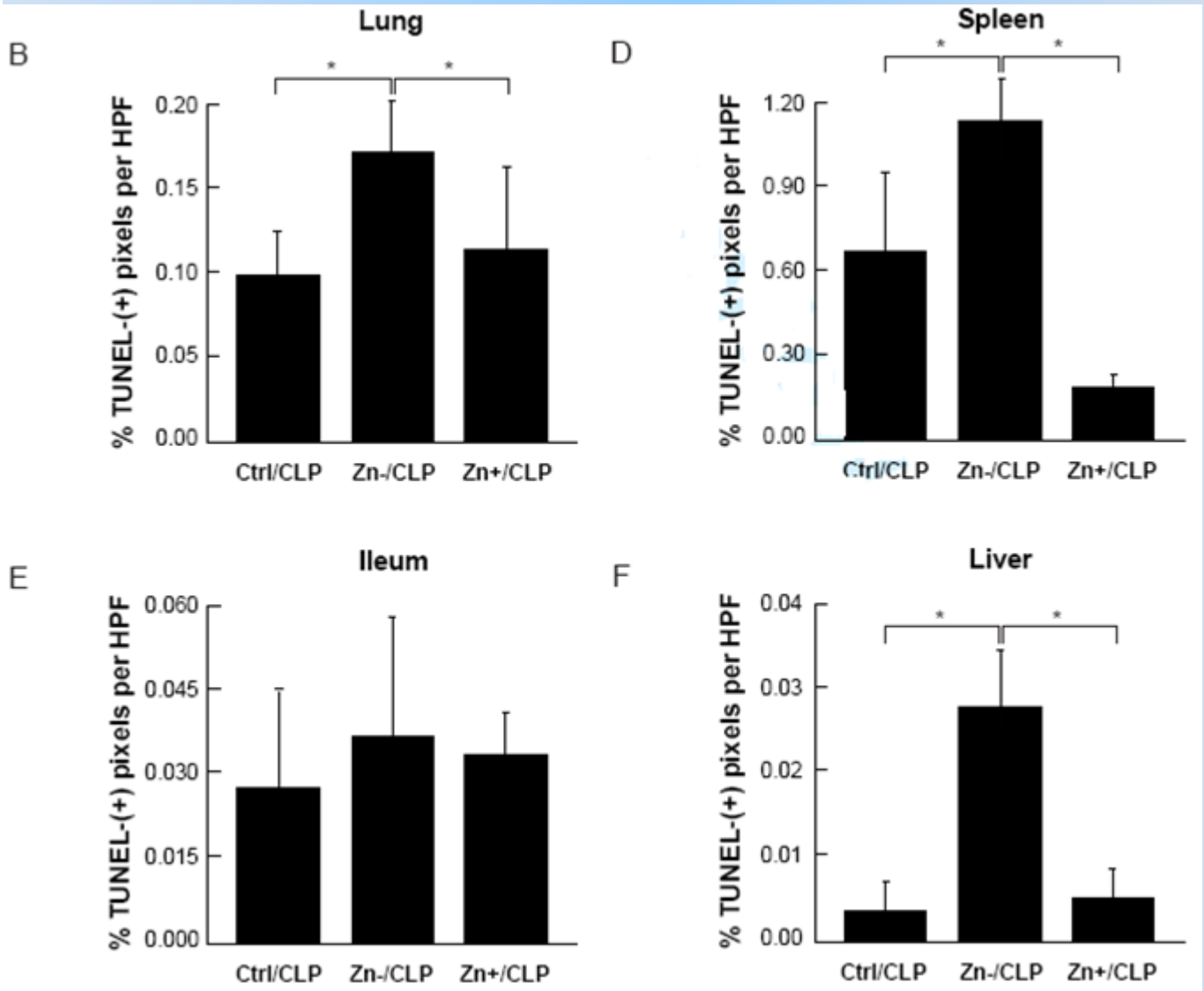
None of sham-op animals died or developed signs of organ damage.

Zinc supplement normalized inflammatory response, greatly ↓ tissue damage, and significantly ↓ mortality.

Zinc deficiency increases sepsis mortality

Knoell DL et al, 2009 CCM

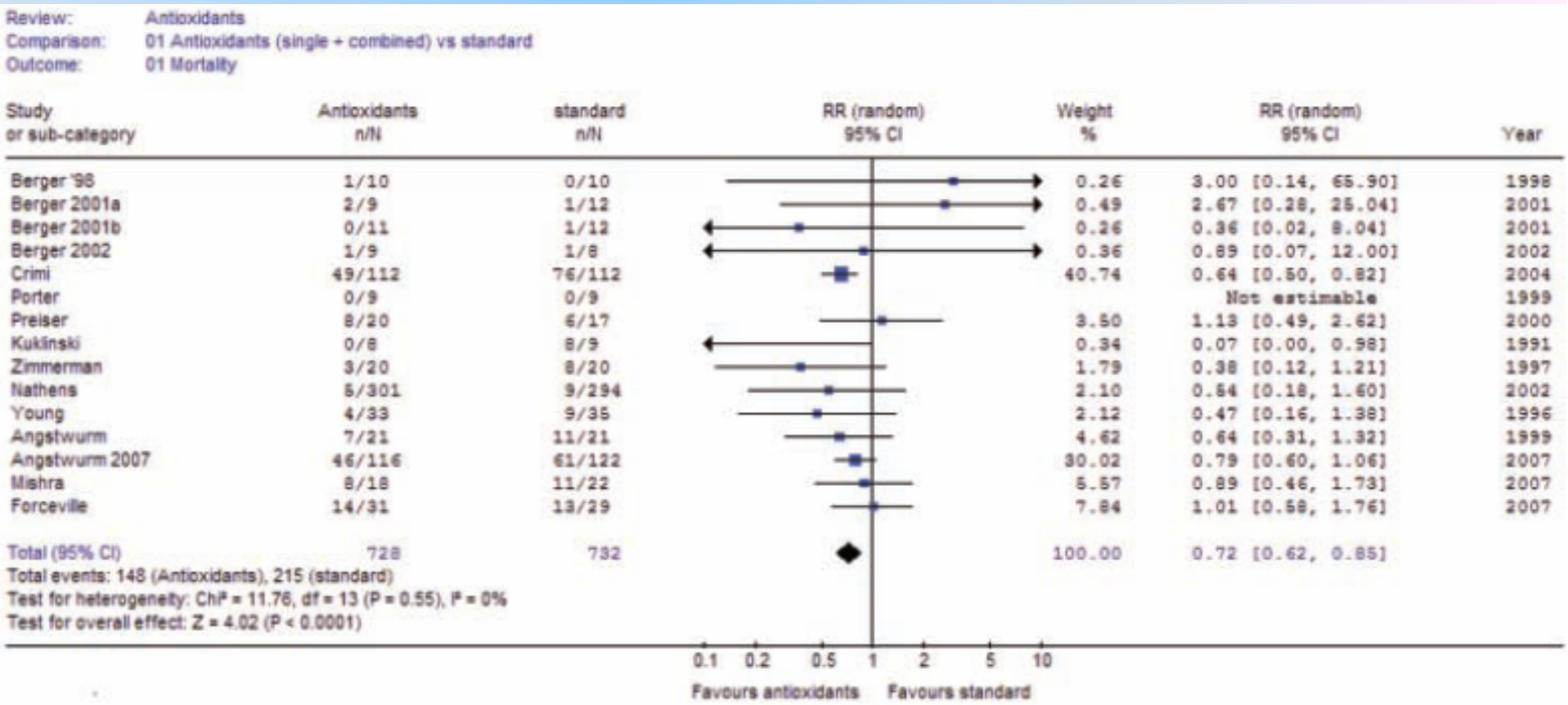
Modulation of cellular tissue injury by zinc status.



cell apoptosis in representative lung (*A*, *B*), spleen (*C*, *D*), ileal (*E*), and liver (*F*) tissues: (*Zn/CLP*) animals demonstrated an ↑ frequency of transferase-mediated dUTP-biotin nick end labeling-positive cells compared with the control

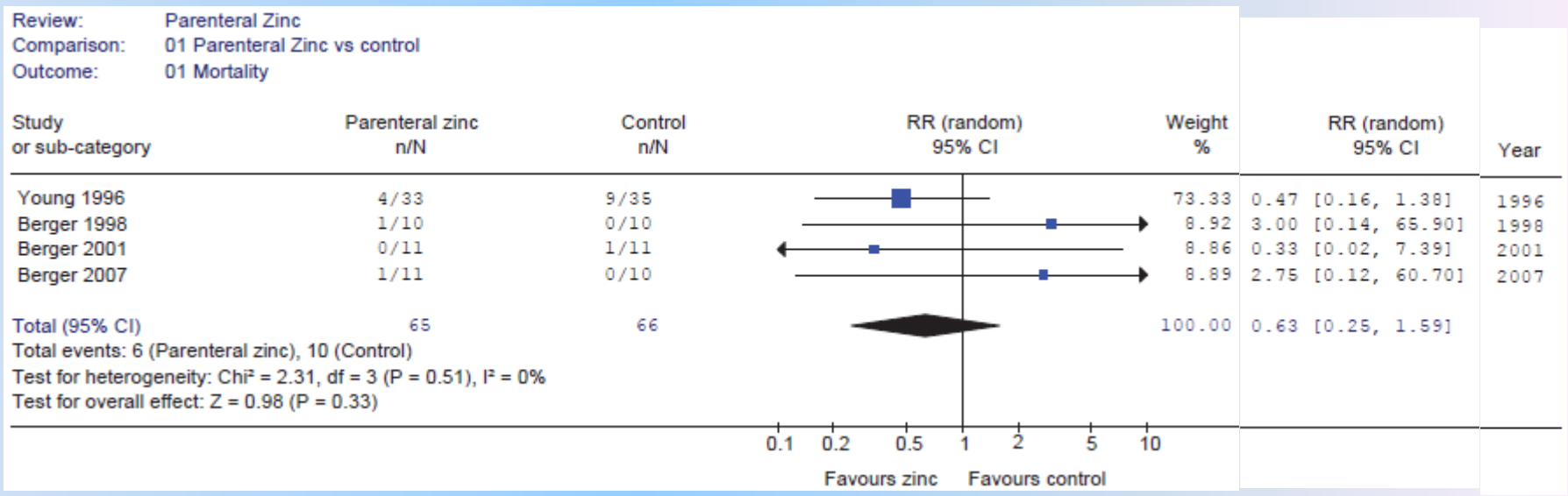
Zinc supplements in critically ill

Heyland et al, *JPEN 2008;32:509*



Zinc supplements in critically ill

Heyland et al, JPEN 2008;32:509



Risk ratio (RR) and associated 95% CI for the effect of zinc supplementation on mortality of critically ill patients.

TE substitution in burns at CHUV
Summary of clinical & biological effects

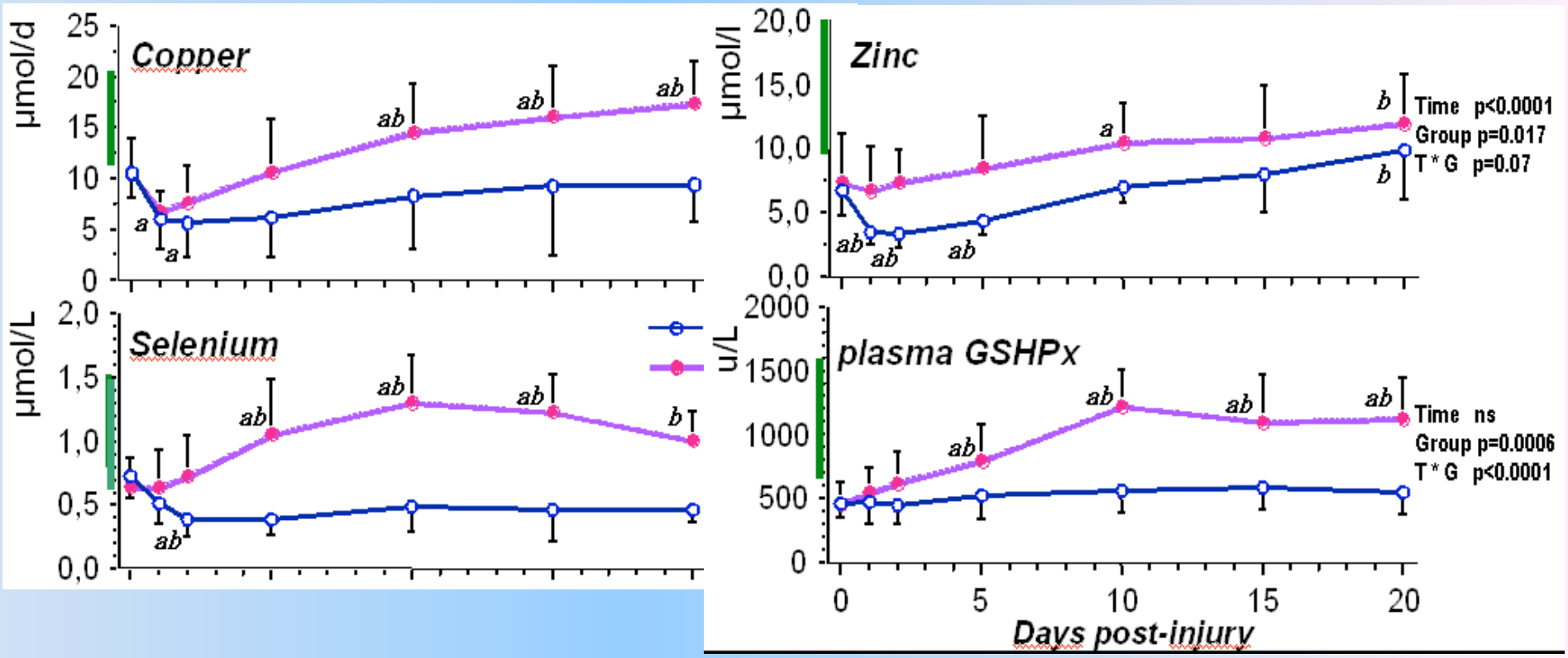
Normalized plasma TE levels	Nutrition 1994 →AJCN 2007
Normalized plasma GPX	Nutrition 1994 →AJCN 2007
↑ Immune response (PMN, PHA)	Nutrition 1994, 10: 327
↓ Lipid peroxidation (MDA)	Burns, 1995, 21:507
↓ Normalized length of stay	Clin Nutr, 1996, 15: 94
↓ Infectious complications	Am J Clin Nutr 1998 [illegible]365
↓ Nosocomial pneumonia	Crit Care 2006 10:R153
Normalized skin TE levels	Am J Clin Nutr, 2007 *85:1293*
↓ Protein catabolism	Am J Clin Nutr, 2007 *85:1301*
↑ Graft take	Am J Clin Nutr, 2007 *85:1301*
↓ Surgery requirements	Am J Clin Nutr, 2007 *85:1301*

Not only AOX effects

Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations[1–3]

Mette M Berger, Malcolm Baines, Wassim Raffoul, Messod Benathan, René L Chiolero, Chris Reeves, Jean-Pierre Revelly, Marie-Christine Cayeux, Isabelle Sénéchaud, and Alan Shenkin

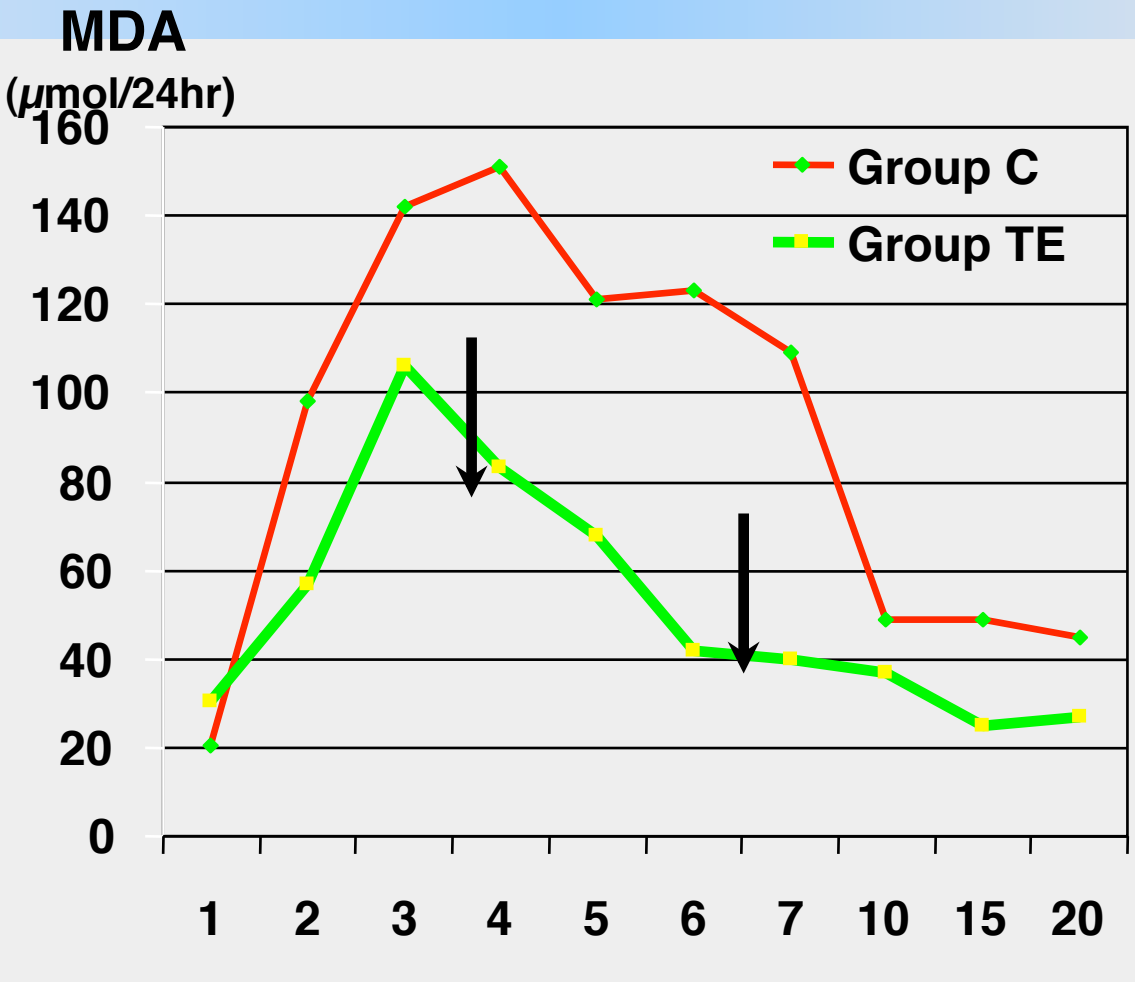
Mean plasma TE over time



Am J Clin Nutr 2007; 85: 1293

Accelerated MDA decay with trace elements

Berger & Chiolero, Burns, 21: 507, 1995

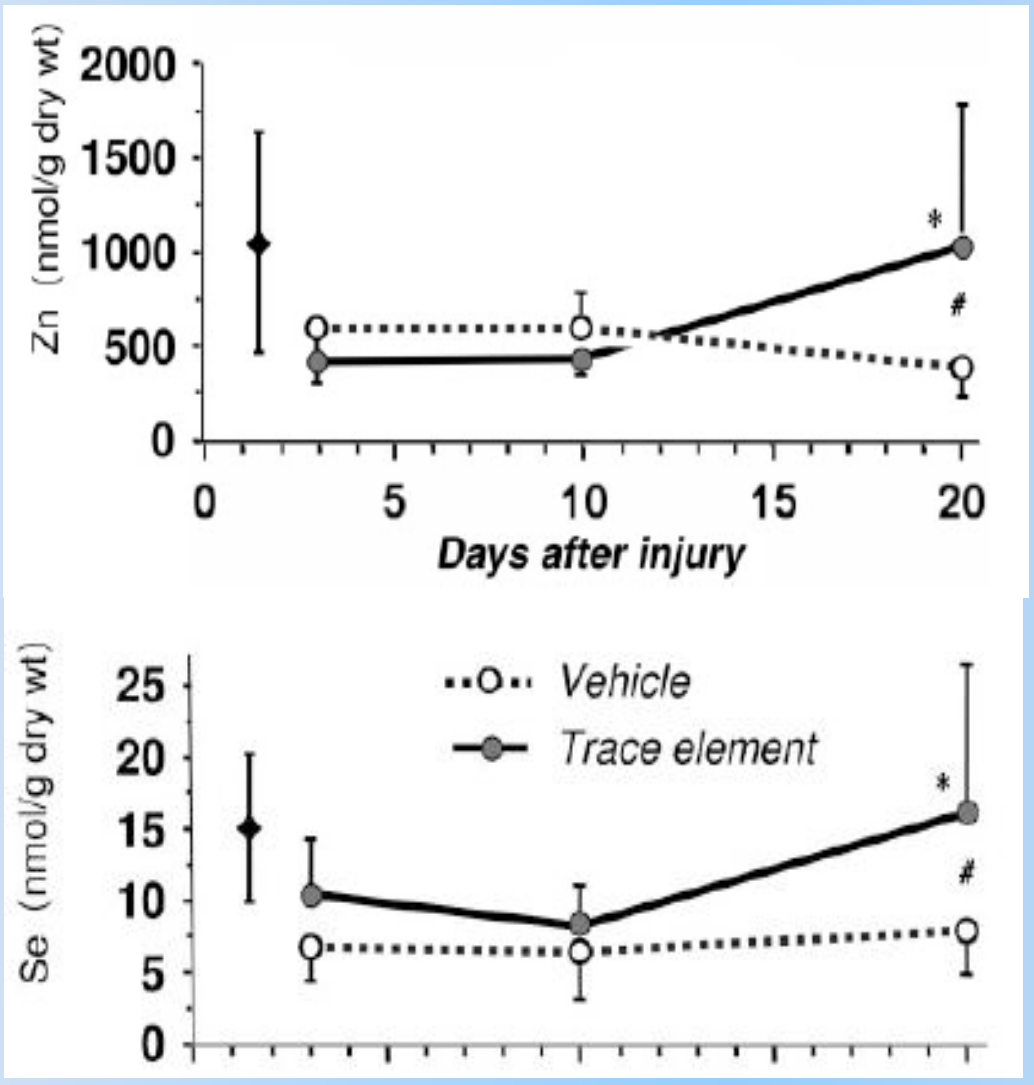


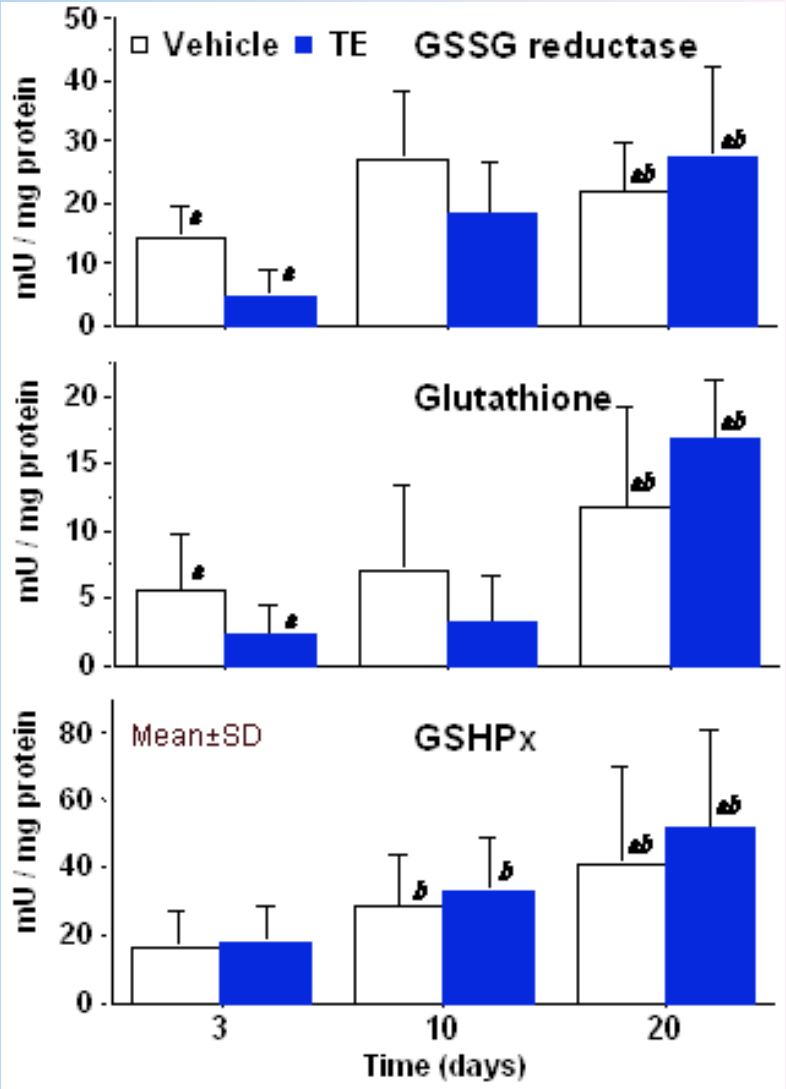
Design: PCT
11 patients (5 / 6)
BSA 42 / 43 %
Group control: ø
Group TE:
Cu,Se,Zn
Urine: 24 hr coll.
$p<0.03$

Substitution

TE after major burns increase [burned skin] and modulate local protein metabolism

Berger et al, Am J Clin Nutr 2007; 85: 1301



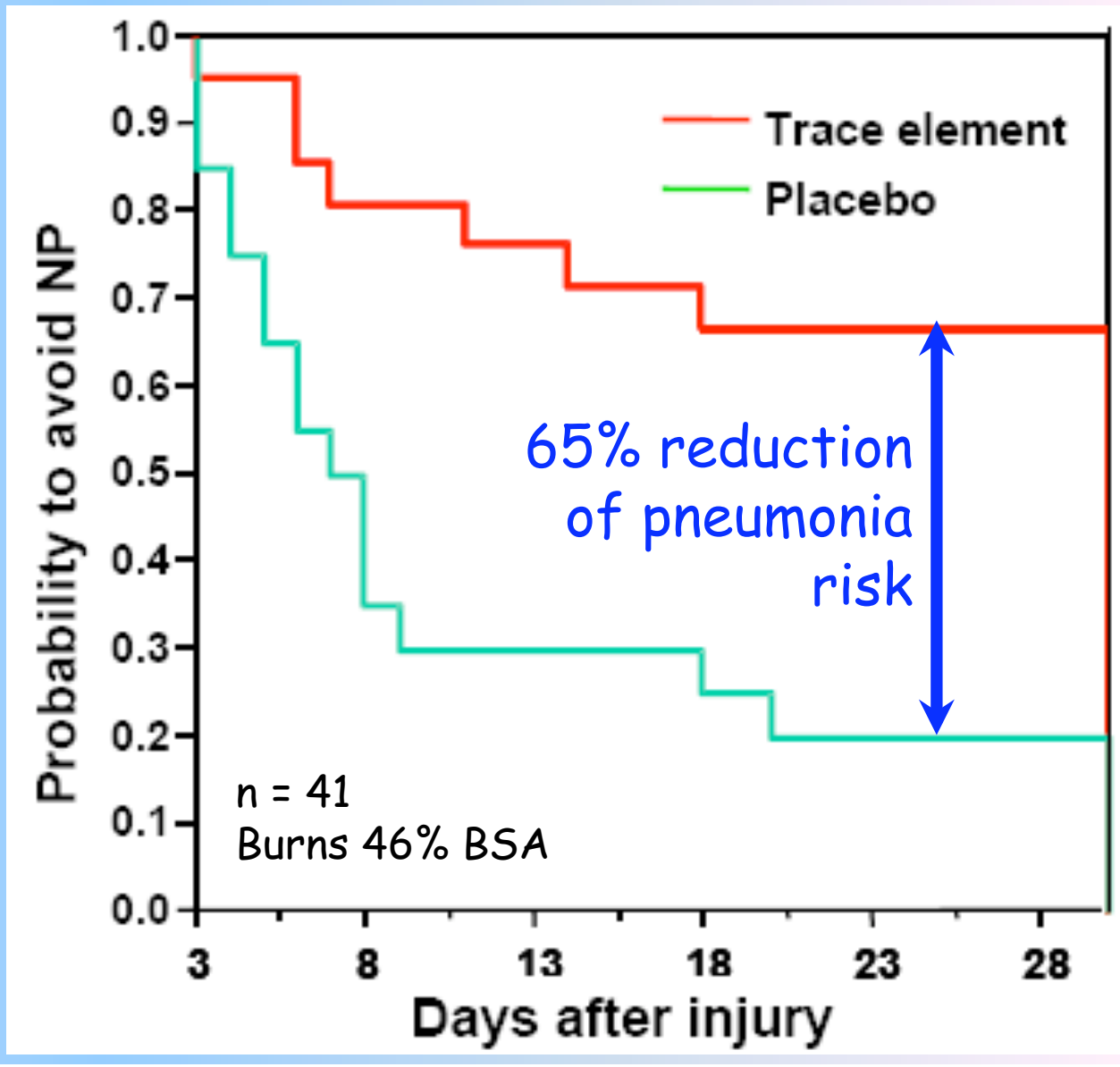


Trace element (Cu,Se,Zn) substitution in Burns - Reduction of nosocomial pneumonia

Berger et al, 2006, Crit Care 10:R153

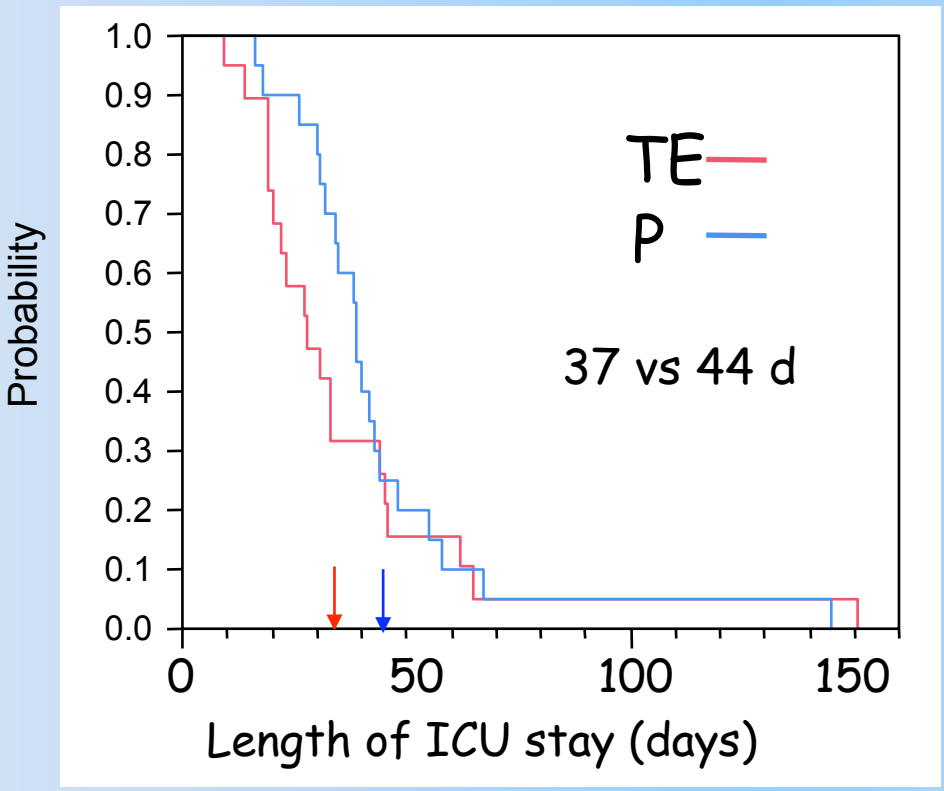
Aggregation of 2 consecutive Randomized Trials → IV
- Cu 3 mg
- Se 300 mcg
- Zn 30 mg

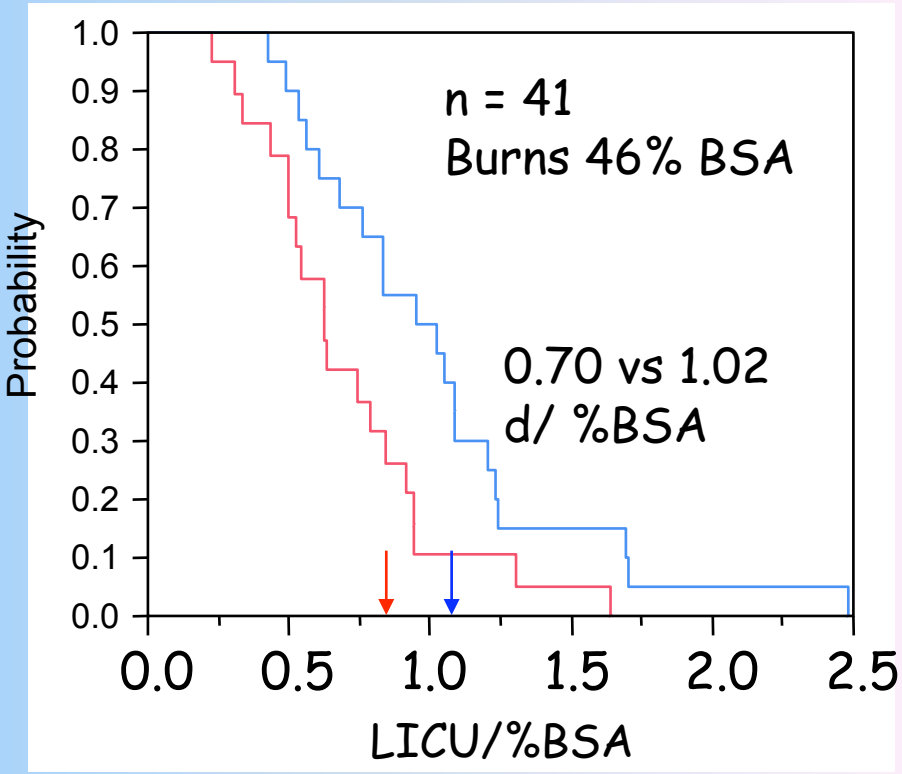
Log Rank
p=0.0014
Wilcoxon
p=0.0019



Length of stay: PRCT TE/placebo

Berger et al, Crit Care 2006, 10:R143





Test	Chi2	DF	Prob>Chi2
Log-Rank	0.4406	1	0.5068
Wilcoxon	2.4457	1	**0.1179**

Tests Between Groups

Test	Chi2	DF	Prob>Chi
Log-Rank	5.3770	1	**0.0204**
Wilcoxon	5.5177	1	**0.0188**

TE substitution in trauma / cardiac surgery patients at CHUV

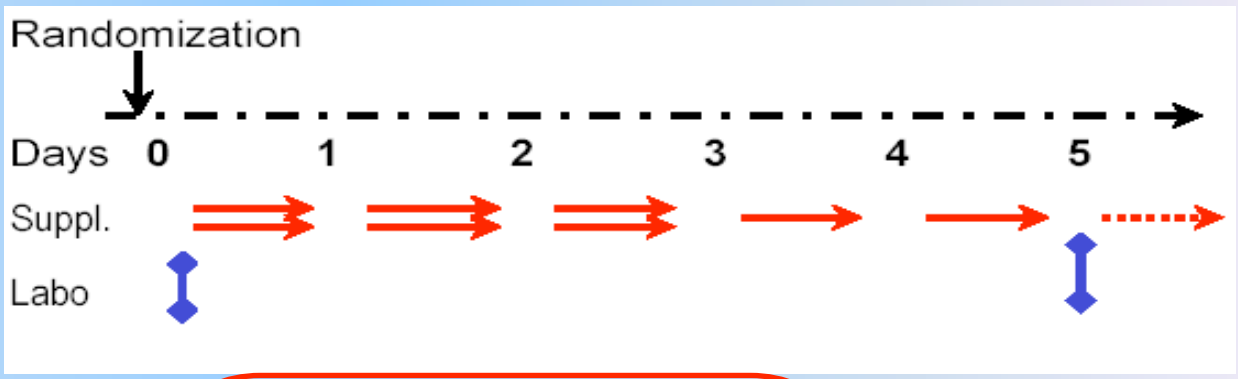
Normalized plasma TE levels	ICM 2001;*27: 91*
Normalized thyroid hormones	ICM 2001
↑ Antioxidants	Nutr Res 2001
↓ Hospital length of stay	Crit Care 2008

Not only AOX effects

5 days AOX supplements in 200 ICU patients

Berger et al Crit Care 2008; 12:R101

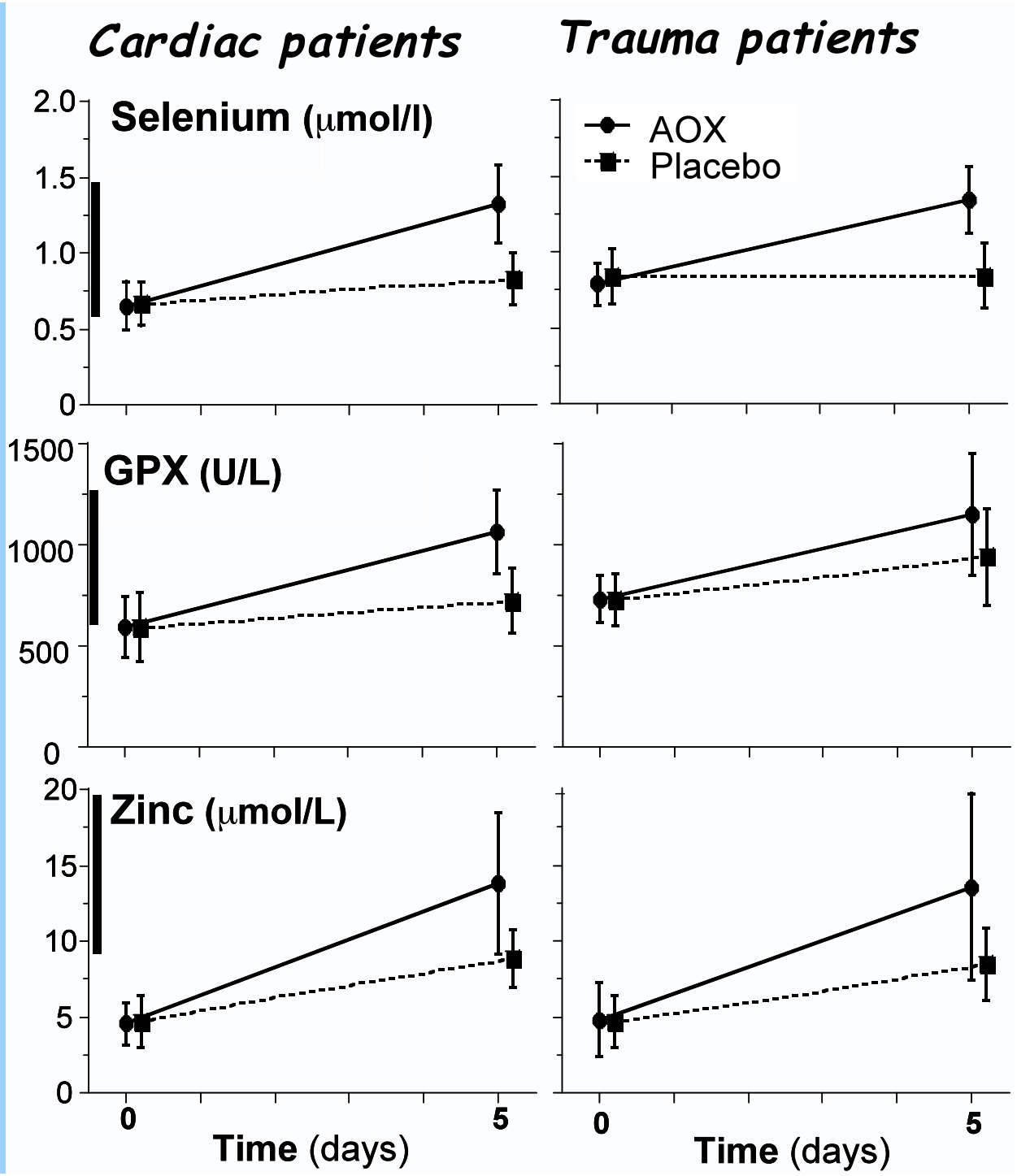
Profil agressé



	Daily dose D1+D2 Double dose	Daily dose D3-D4-D5 Single dose	Comparison TPN dose D1-2/ D3…
Selenium	540 µg	270 µg	**12x / 6x**
Zinc	60 mg	30 mg	**12x / 6x**
Vitamin C	2,7 g	1,6 mg	**34x / 20x**
Vitamin B1	300 mg	100 mg	**120x / 40x**
Vitamin E	600 mg NG + 12.8* mg iv	300 mg NG + 6.4* mg iv	**40x / 20x 2x / 1x**

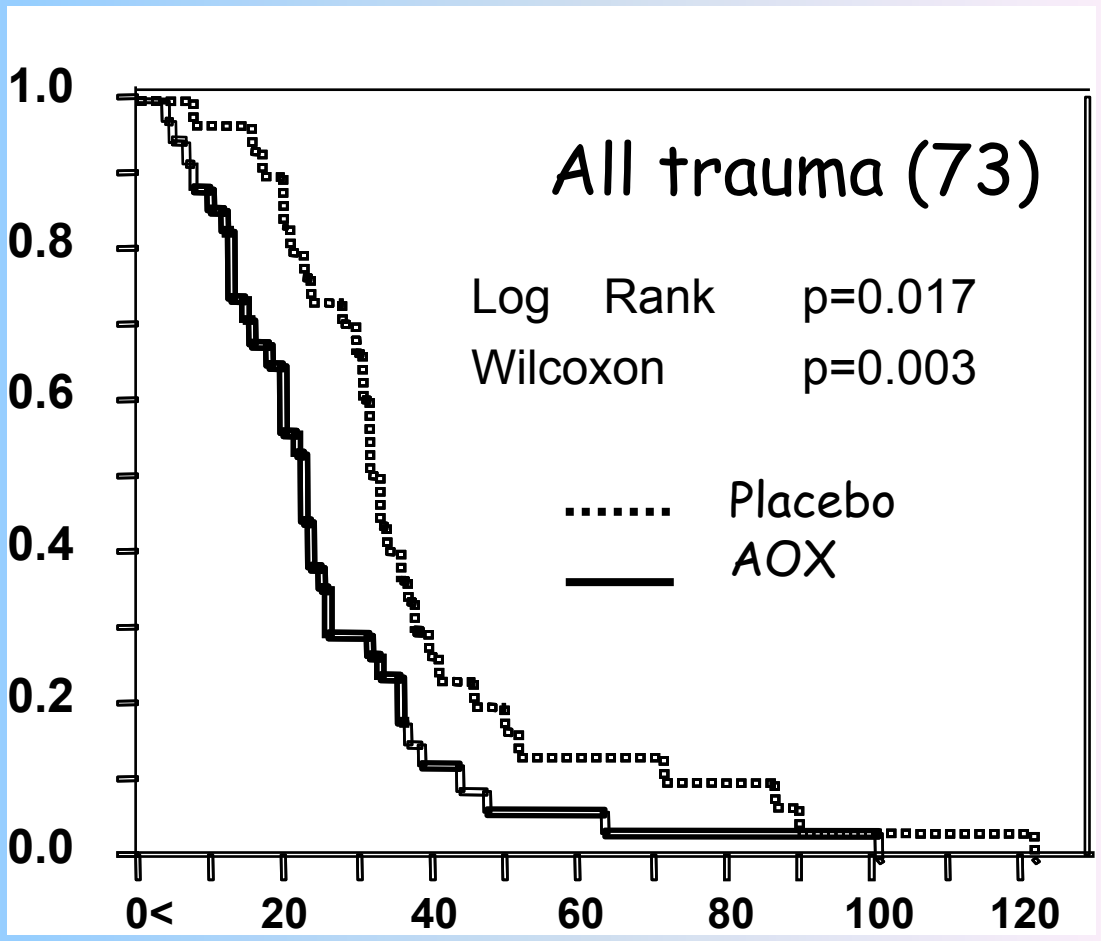
5 days iv AOX supplements in 200 ICU patients

Berger et al
Crit Care 2008;
12:R101



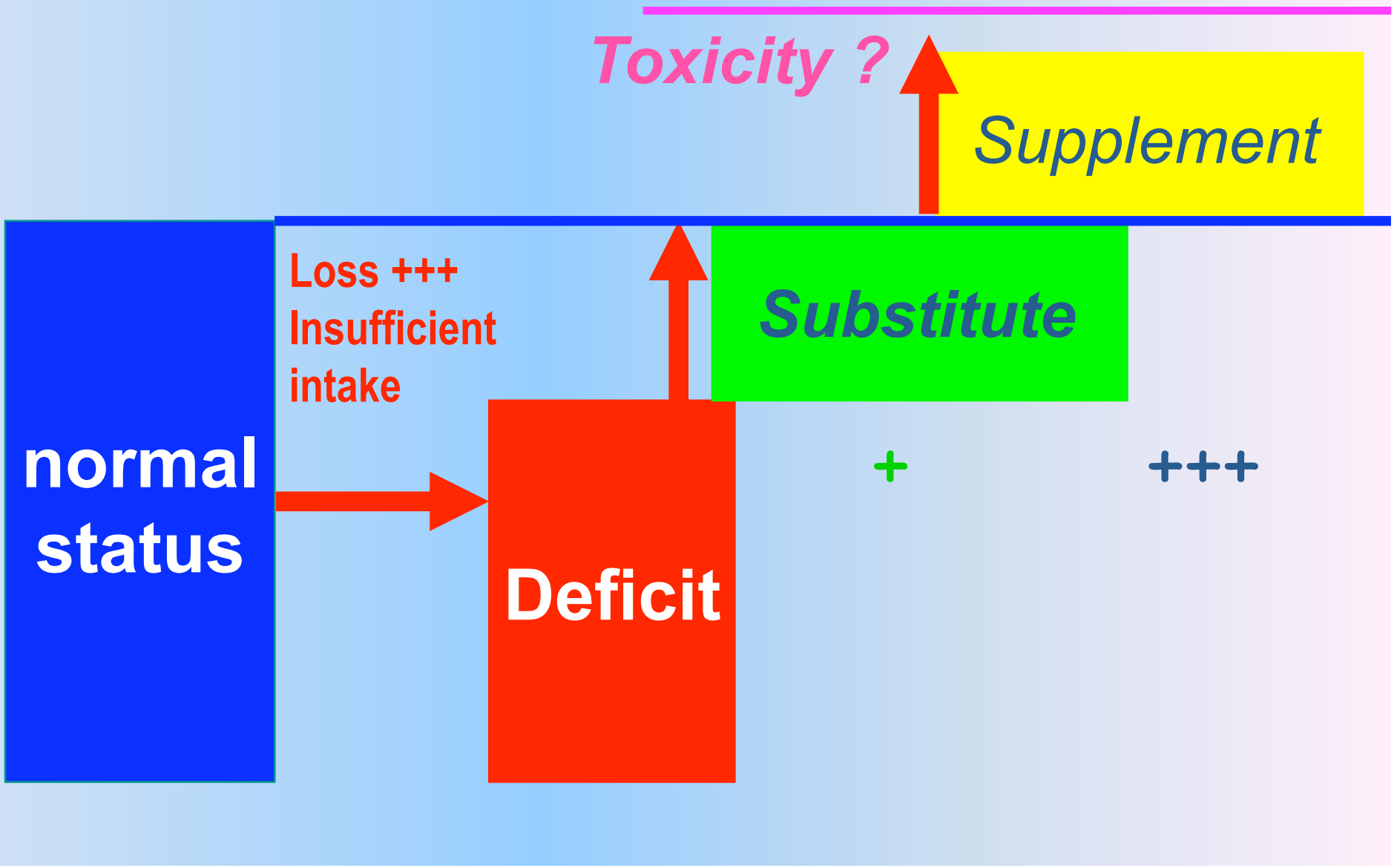
5 days iv AOX supplements in 200 ICU patients

Berger et al
***Crit Care* 2008; 12:R101**



- 11 days in hospital

Substitute or supplement?
2 distinct strategies – 2 aims



Micronutrient standard policy – CHUV ICU

Type de patient / Type de Nutrition	**Patient agressé et/ou dénutri** (Niveau C) Polytrauma, TCC sévère, Hépatopathie fulminante, sepsis sévère, ARDS, MODS, Transplantation hépatique et pulmonaire, Choc cardiogène, mucoviscidose, BPCO sévère, maladies inflammatoires du tube digestif
Nutrition entérale	Profil agressé-NP : J1 à J6 Profil standard dès J7 **Polytraumatisé, avec ou sans TCC :** +500 ml Intestamine de J1 à J10
Nutrition parentérale	Profil agressé-NP dès début nutrition IV
Alimentation per os	Profil agressé-NP : J1 à J6 Profil standard dès J7

Profil standard : 1 cp multi-vitaminé et multi-minéraux (Supradyn®) : per os ou entéral

Profil agressé-NP: **ET** : 1 fiole solution ET (Décan®) + 100 µg Sélénium + 5 mg Zinc : injecter le Zinc et le Sélénium dans la fiole de Décan. Overs central venous line 6h.

Vit. :1 amp. solution multi-vitaminée (Cernévit®) + 500 mg vit. C (vitamine C Streuli®) + 100 mg vit. B1 (Benerva®). vvc dans 100 ml de Glucose 5% en 6h (0h-6h), after ET.

Vit. :Vit. K (Konakion®) : 10 mg 1x par semaine (le lundi).

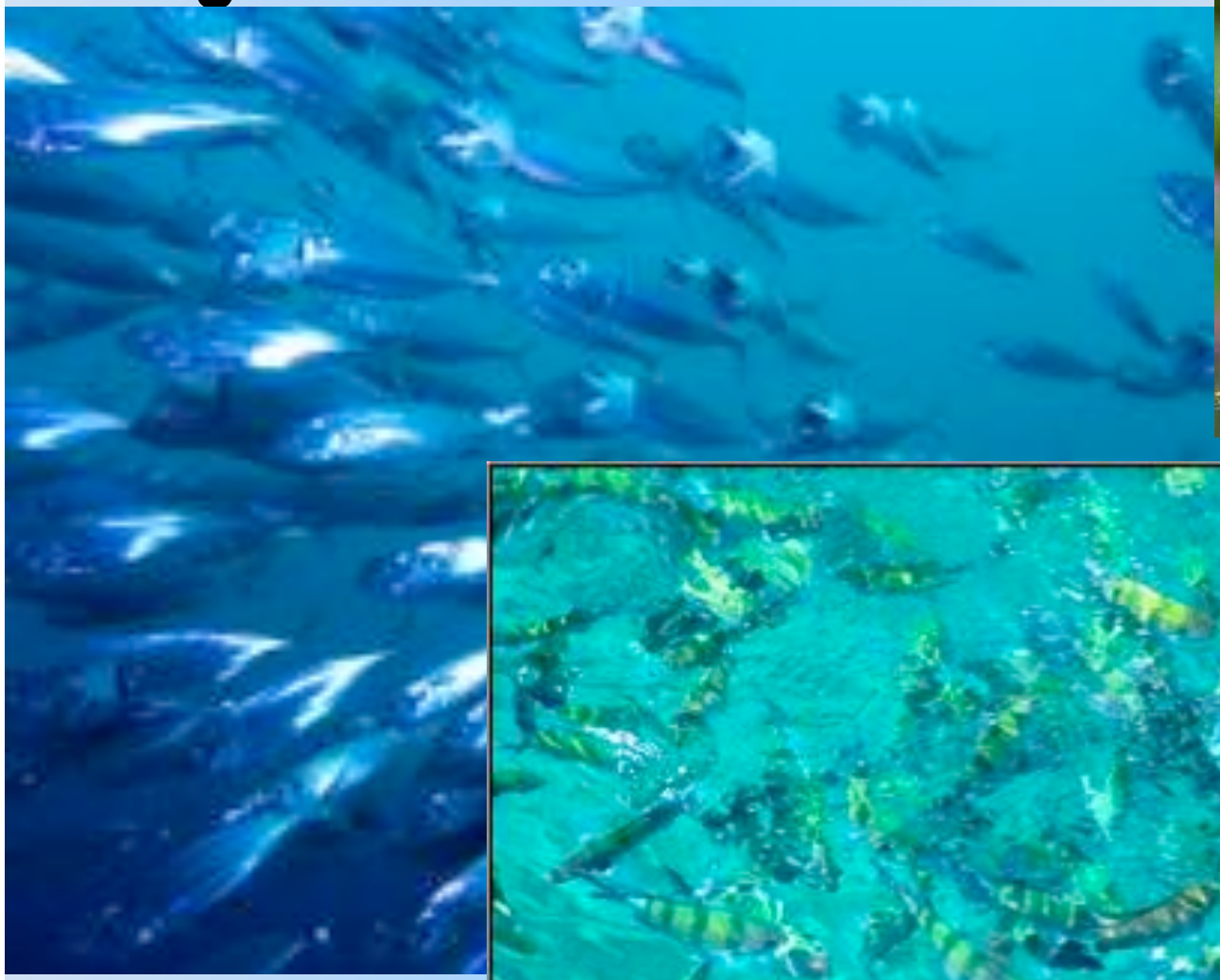
Profil Brûlé : **ET** :1 Flex ET-Plus Pharmacie CHUV (3.75 mg cuivre, 375 µg sélénium, 37.5 mg zinc, 1200 mg phosphate). Flex de 250 ml dans NaCl 0,9%. Central line in18h

ET :1 EO - ET (Décan®) : en 6h (18h-0h).

Vit. :1 amp. solution multi-vitaminée (Cernévit®) + 500 mg vit. C (vitamine C Streuli®) + 100 mg vit. B1 (Benerva®). vvc dans 100 ml de Glu 5% en 6h (0h-6h), à la suite des ET,

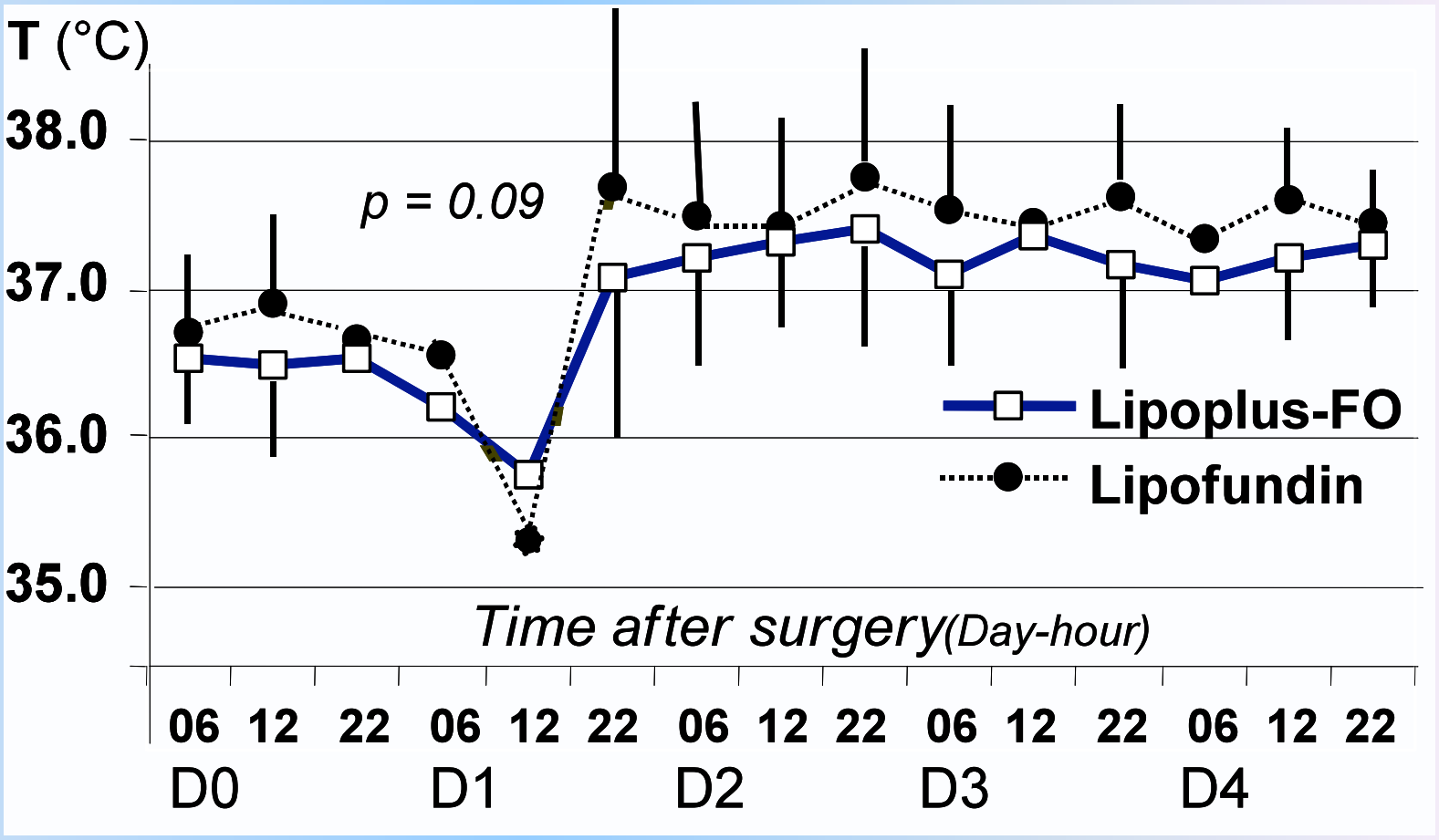
Vit. :100 mg vitamine E (Vitamine E Streuli ®) : per os ou entéral

Omega-3:
Borage – Fish from Cold Waters

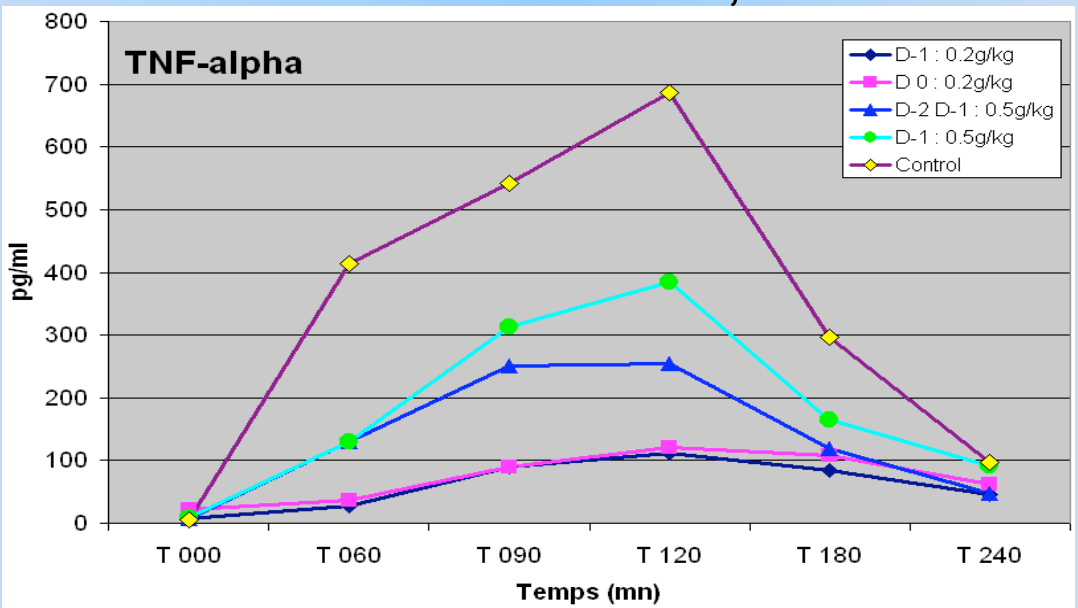


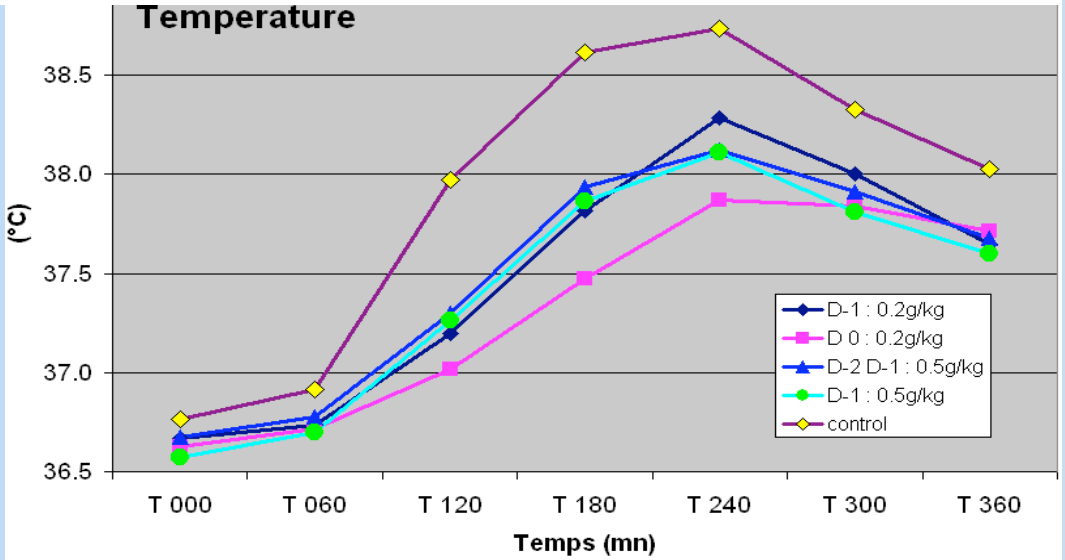
Fish oil after abdominal aorta aneurysm surgery

Berger et al, EJCN, 2008



FO blunts response to Endotoxin in healthy subjects
Dose finding
Pittet et al, ICM 2010





Omega-3 fatty acids improve the diagnosis -related clinical outcome

Heller et al 2006

Prospective, open label, multiple-centre trial.

PATIENTS : A total of 661 patients from 82 German hospitals receiving total parenteral nutrition for > or =3 days were enrolled in this study.

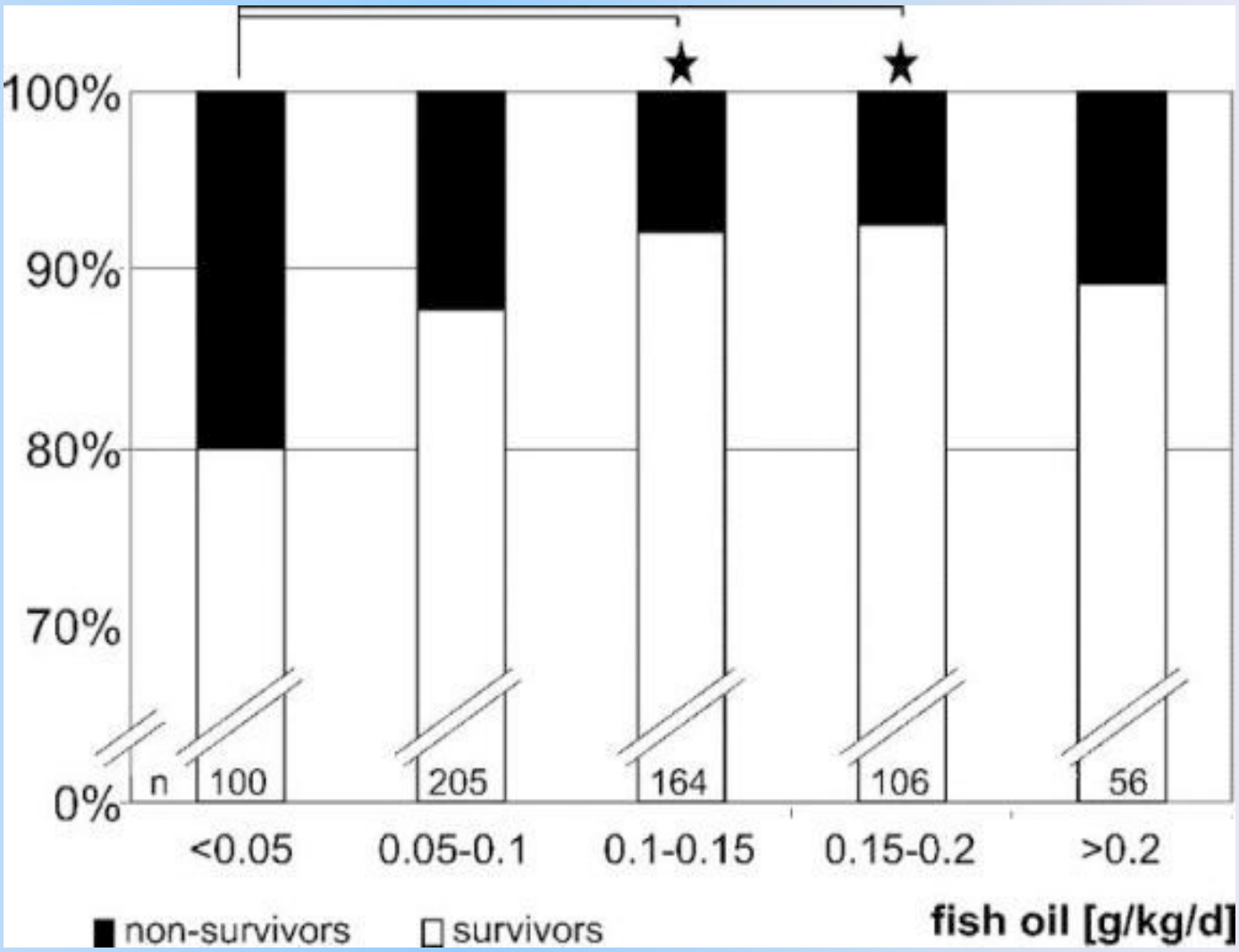
- 255 patients after major abdominal surgery
- 276 with peritonitis and abdominal sepsis
- 16 with non-abdominal sepsis
- 59 after multiple trauma
- 18 with severe head injury, and 37 other diagnoses.

Primary study end point was survival

Secondary end points: length of hospital stay, use of antibiotics with respect to the primary diagnosis and the extent of organ failure.

Omega-3 fatty acids improve the diagnosis-related clinical outcome

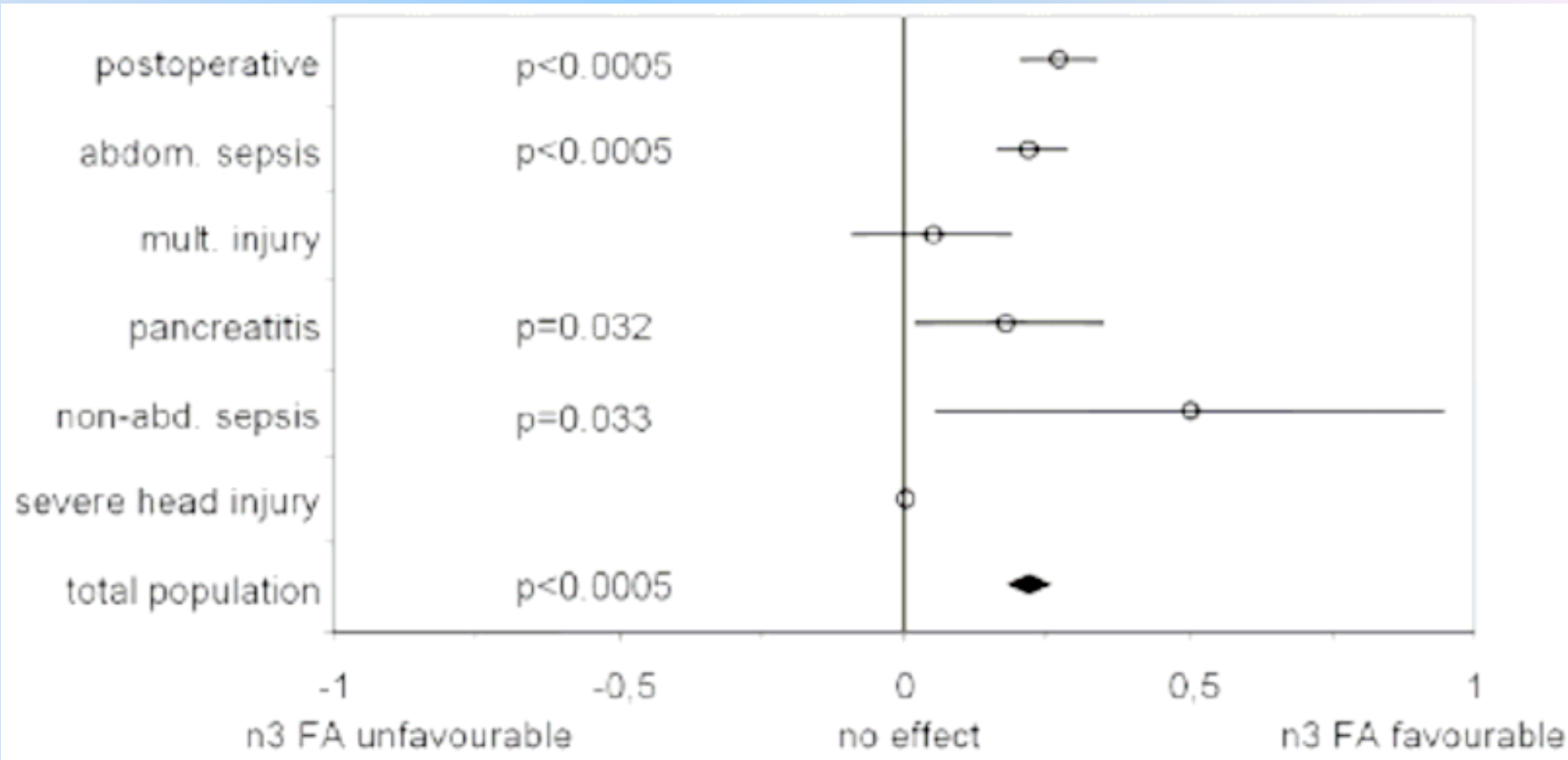
Heller A et al, Crit Care Med 2006 34:972



Survival in % of patients in dose-related subgroups

Omega-3 fatty acids improve the diagnosis-related clinical outcome

Heller AR et al, Crit Care 2006, 34:972



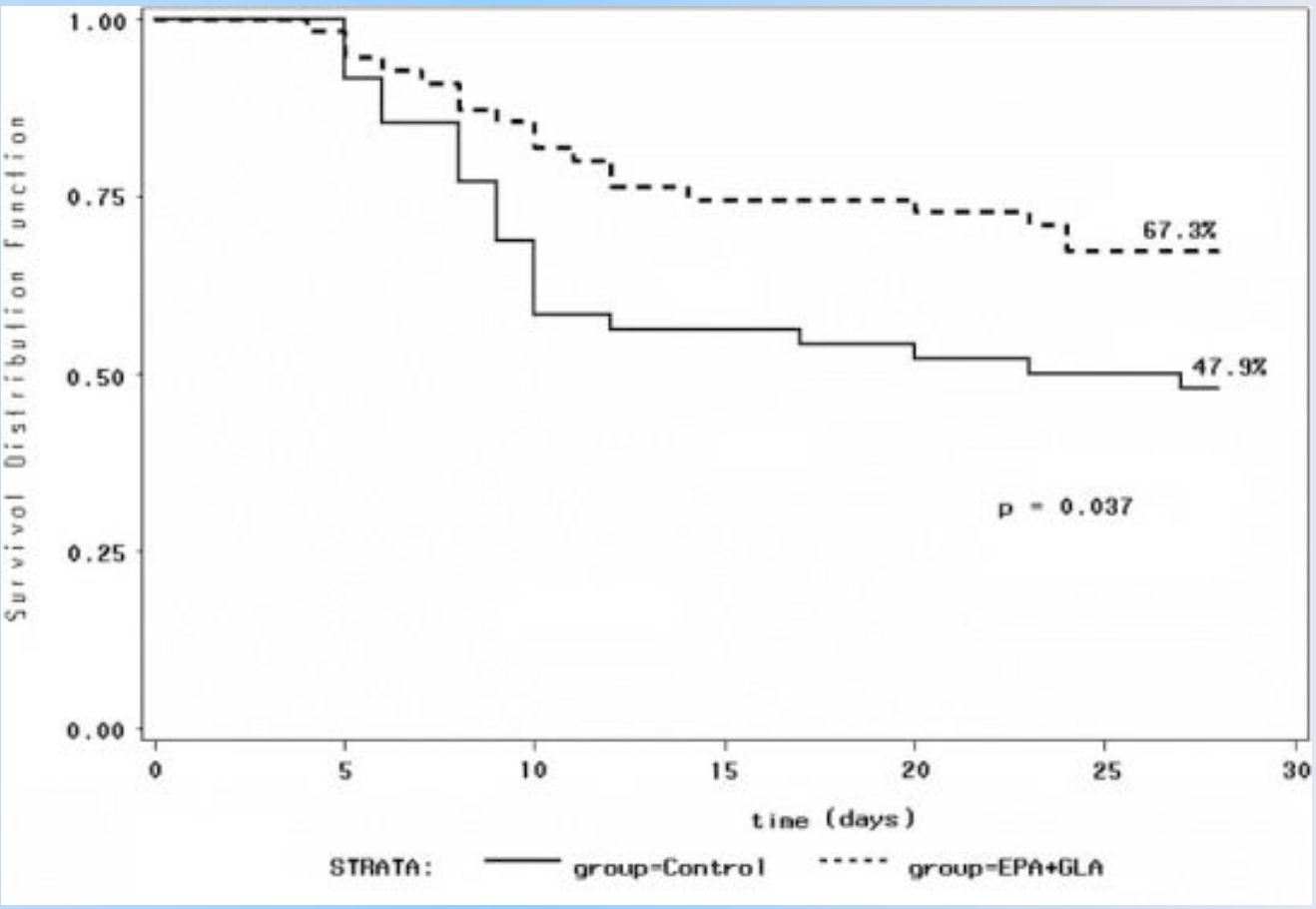
Forrest plot of diagnoses-related effect (mean, 95% CI) on % mortality differences : 661 patients from 82 German hospitals receiving TPN for > or =3 days

n-3 fatty acid may reduce mortality, antibiotic use, and LOS in ≠ diseases.

Effects and effect sizes related to fish oil doses are diagnosis dependent

Effects of EN with EPA, GLA, and AOXs in mechanically ventilated patients with severe sepsis and septic shock

Pontes-Arruda et al, CCM 2005

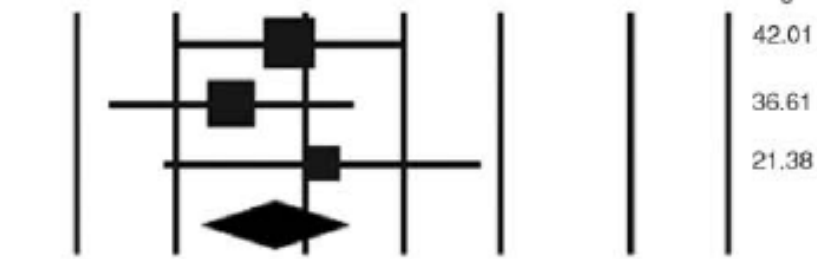


Kaplan-Meier survival curves 28-day period. The EN with EPA and GLA (n=55) was associated with a significantly higher survival compared with control group (n=48) (p = .037 by log-rank test)

Use of an Inflammation-Modulating Diet in Patients With Acute Lung Injury or ARDS: Meta-Analysis Pontes-Arruda et al. JPEN 2008

28-day in-hospital all-cause mortality

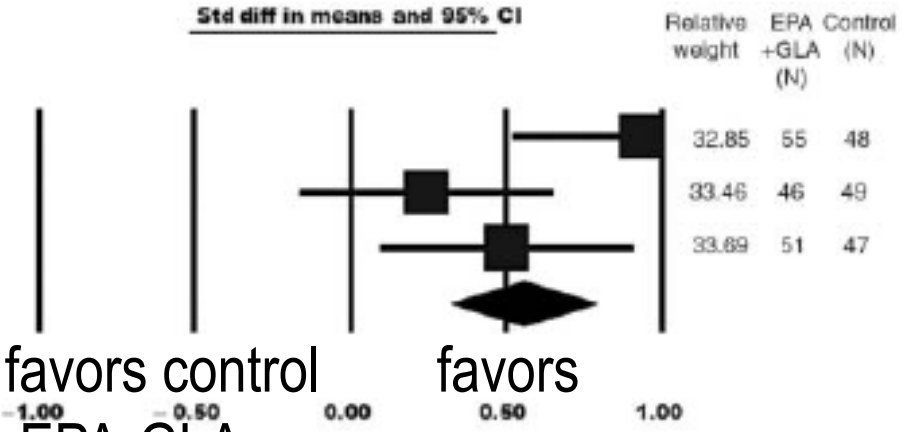
Study name	Odd ratio	Lower limit	Upper limit	Z Value	P Value	Relative weight	EPA+GLA (n/N)	Control (n/N)
Pontes-Arruda et al	0.448	0.201	0.995	−1.973	.049	42.01	18/55	25/48
Singer et al	0.295	0.126	0.695	−2.793	.005	36.61	13/46	28/49
Gadek et al	0.563	0.184	1.725	−1.006	.315	21.38	6/51	9/47
Fixed effects	0.404	0.241	0.678	−3.434	.001			



⬇⬇ by 60%

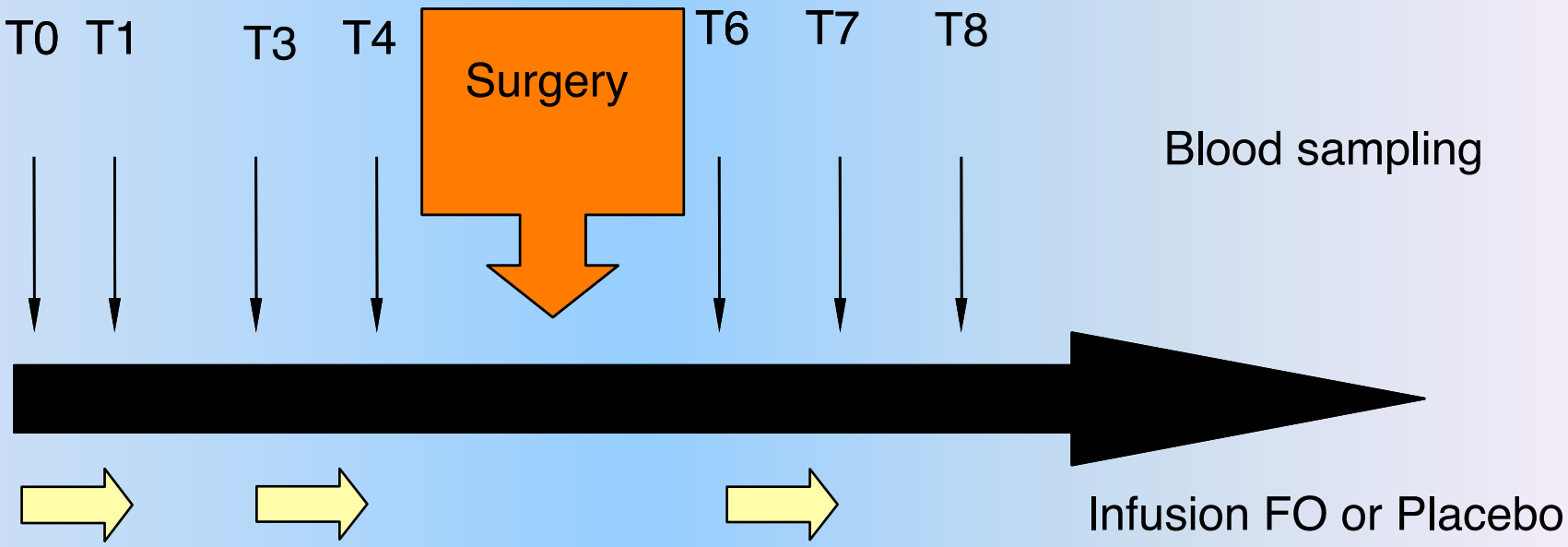
Ventilator-free days

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z Value	P Value	Relative weight	EPA +GLA (N)	Control (N)
Pontes-Arruda et al	0.933	0.208	0.043	0.525	1.340	4.485	.0000	32.85	55	48
Singer et al	0.242	0.206	0.042	−0.161	0.646	1.176	.2395	33.46	46	49
Gadek et al	0.501	0.205	0.042	0.099	0.904	2.442	.0146	33.69	51	47
Fixed effects	0.556	0.119	0.014	0.323	0.790	4.669	.0000			



⬆ by 5 d/28 d

Short FISH OIL infusions modulate cardiovascular and metabolic response in patients undergoing CABG surgery: preliminary data



Intervention Timings: 3 infusions 0.2 g/kg

Short FISH OIL infusions modulate cardiovascular and metabolic response in patients undergoing CABG surgery: preliminary data

Patients

	Mean	and SD
	Placebo	FO
Number	11	11
Female/ Male	2F/8M	0F/10M
Age	67 ±13	67.5±10
Weight	81.6±13	79.6±12
APACHE II	15.1±2.33	12.6±4.2
SAPS II	29.6±6.3	30.7±8.2
EUROSCORE	3.2±2.3	4.6±2.6
Lenght of mechanical ventilation (hour)	23.2±27.9	9.2±3.7
Lenght of ICU stay (hours)	55.7±35.1	41.5±28.3
Amount of bleeding first 24 hrs (ml)	1120±1218	857±400

Short FISH OIL infusions modulate cardiovascular and metabolic response in patients undergoing CABG surgery: preliminary data

platelets incorporation

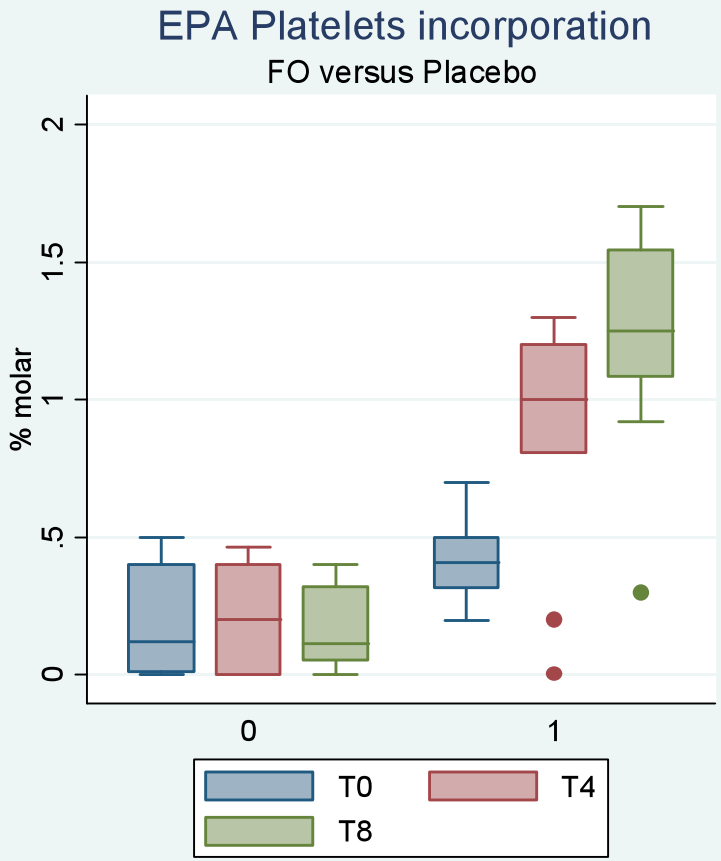


Fig 1: EPA Platelets incorporation of 24 sujets

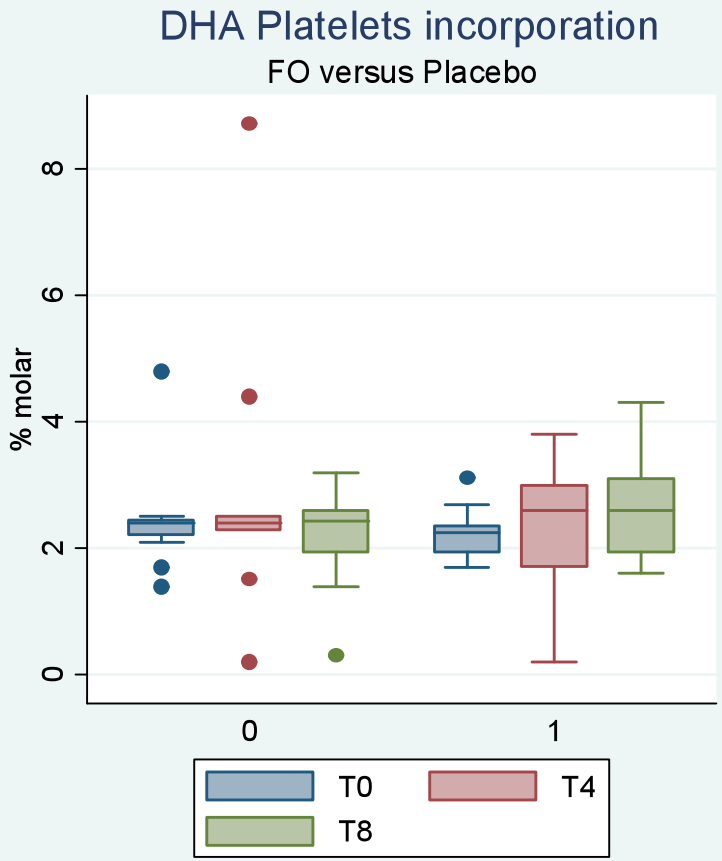


Fig 2: DHA Platelets incorporation of 24 sujets

Fig 1: platelets incorporation of 24 sujets

« Cardiac FO »

Tissue EPA incorporation

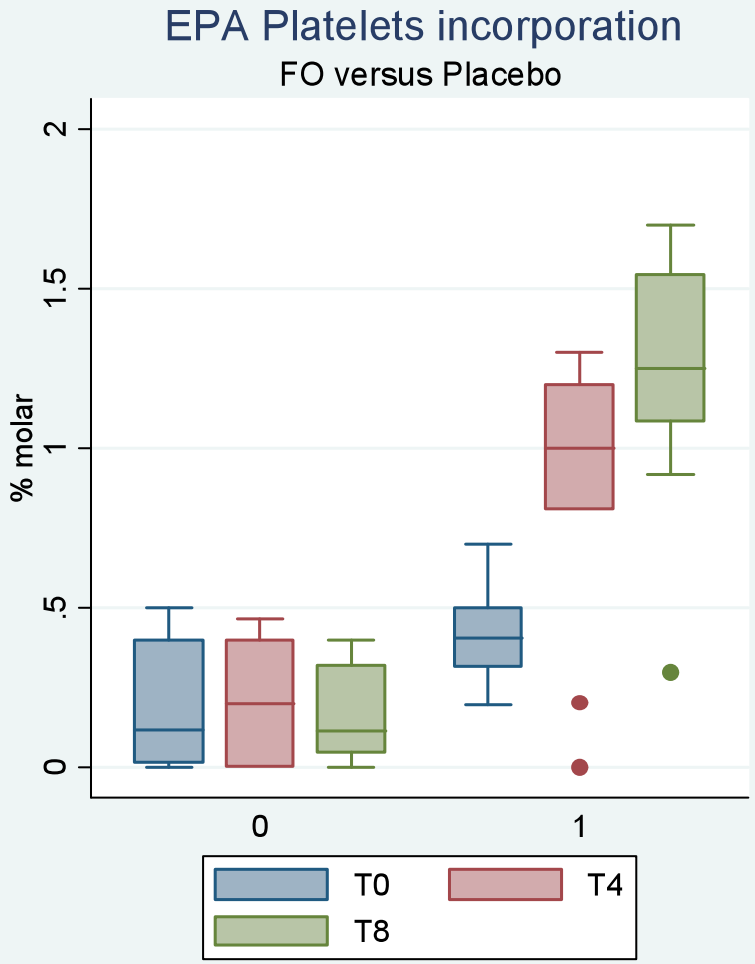


Fig 1: EPA Platelets incorporation of 24 sujets

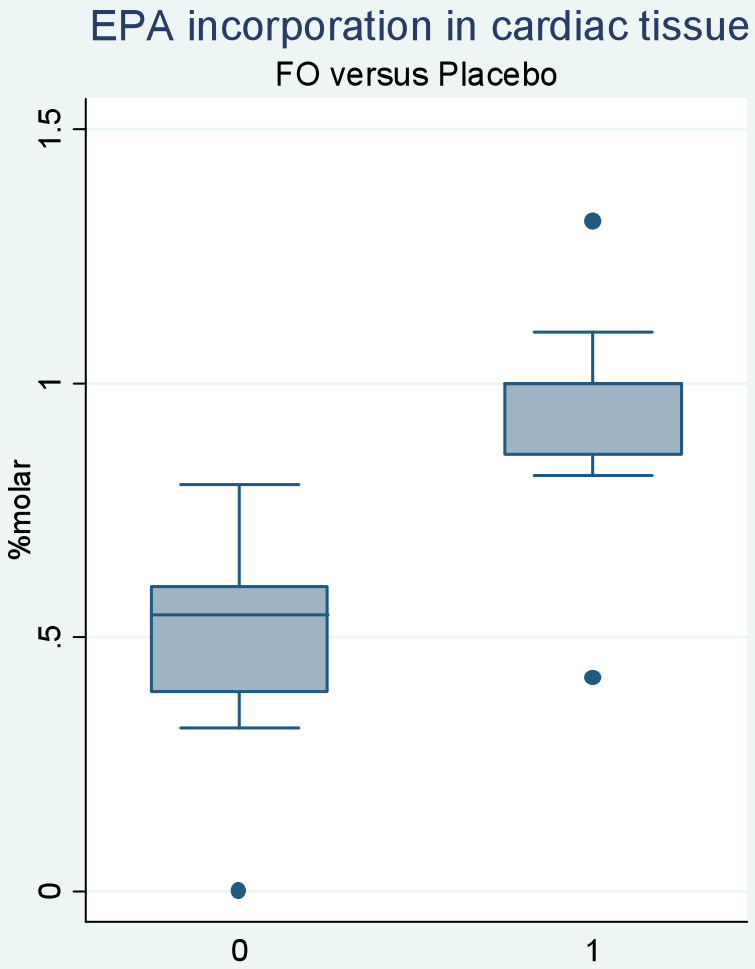
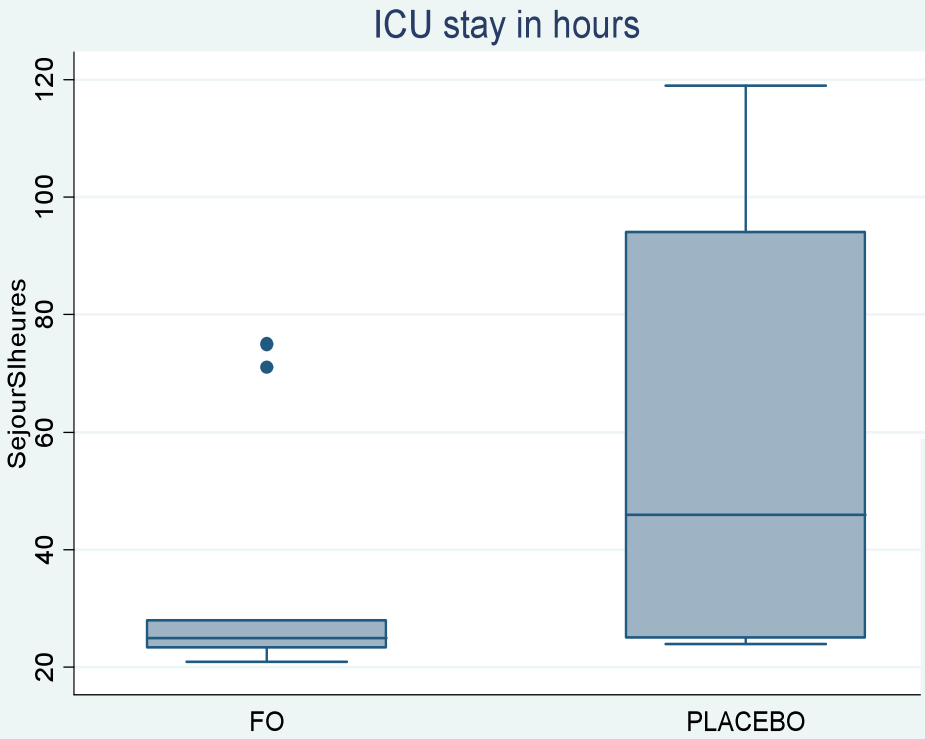
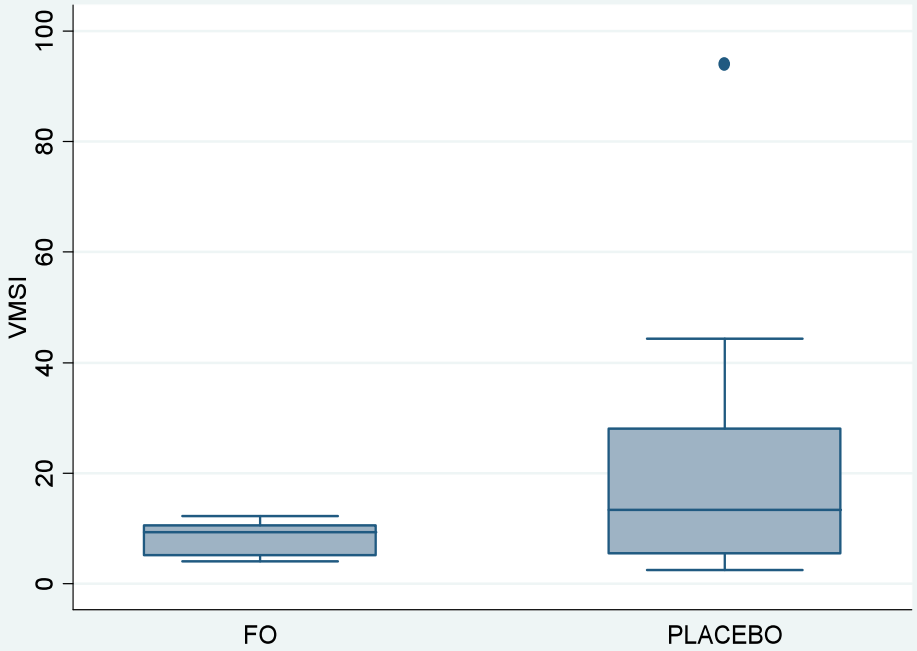


Fig 2: EPA incorporation in cardiac tissue of 24 sujets

highly significant p<0.001

« Cardiac FO »





Lesser variability of clinical evolution

PharmacoNutrition en SI - conclusions

Les patients SI inflammatoires sont à risque +++ de statut suboptimal en micronutriments: Se, Zn + GLN

Qques nutriments se profilent « anti-inflammatoires »

Substitution de déficits aigus/préexistants est logique et prouvée bénéfique

Doses requises pour supplémentation sont « supra nutritionnelles » mais non définies

Doses → 10 x RDA sont probablement « sûres »

PharmacoNutrition en SI – conclusions ’

Plusieurs nutriments sont concernés → voie digestive – existe compétitions pr absorption …

Et .. absorption digestive est variable

Etudes positives sont réalisées par voie I.V.

Qui? Patients inflammatoires

Quand? Phase précoce – 5 premiers jours puis sur indication

Auspices favorables: Se, Zn, GLN, n-3

Lac Léman tôt le matin

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