New treatments in sepsis

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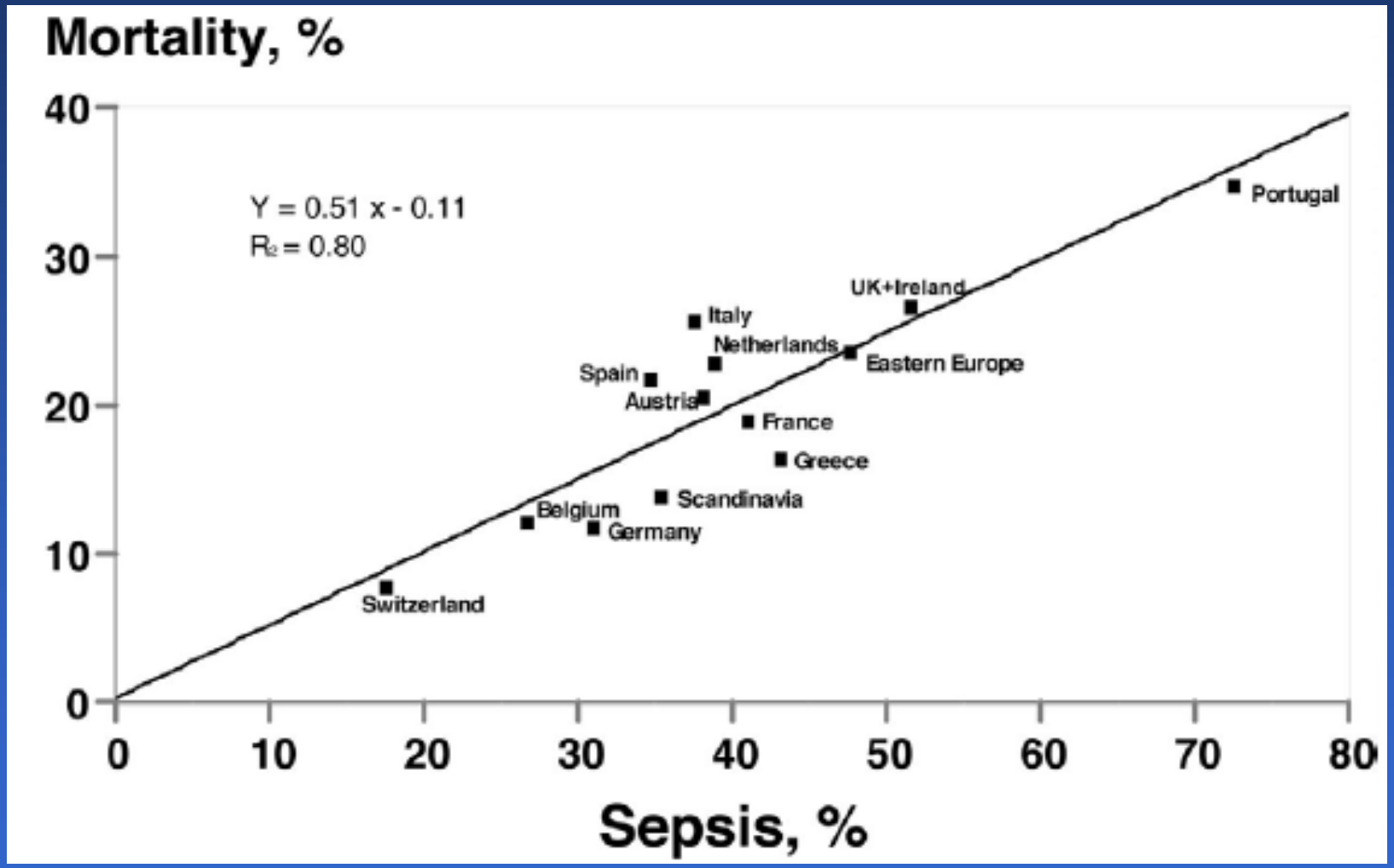
Sepsis on European ICU's

- Overall, **64%** of 3147 patients received antibiotics
- Sepsis identified in **37%** patients
  - **60%** culture positive
  - Gram positive **40%**
  - Gram negative **38%**
  - C albicans **13%**
- Commonest sites of infection:
  - Lung **68%**
  - Abdomen **22%**
  - Blood **20%**
  - UTI **14%**

*Vincent et al, Crit Care Med 2006 **34**:344*

Death from sepsis on European ICU's

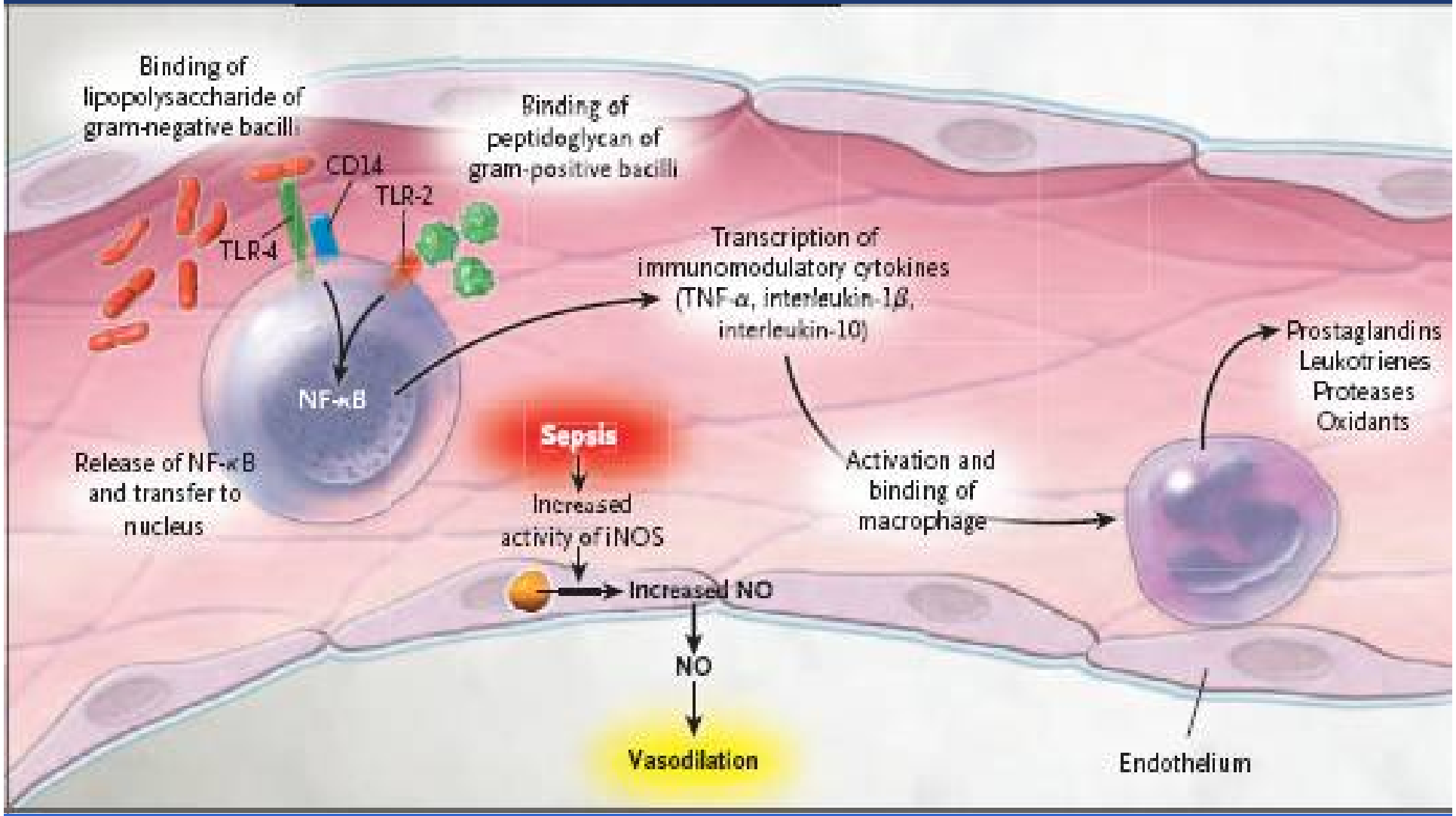


Vincent et al, Crit Care Med 2006 ***34****:344*

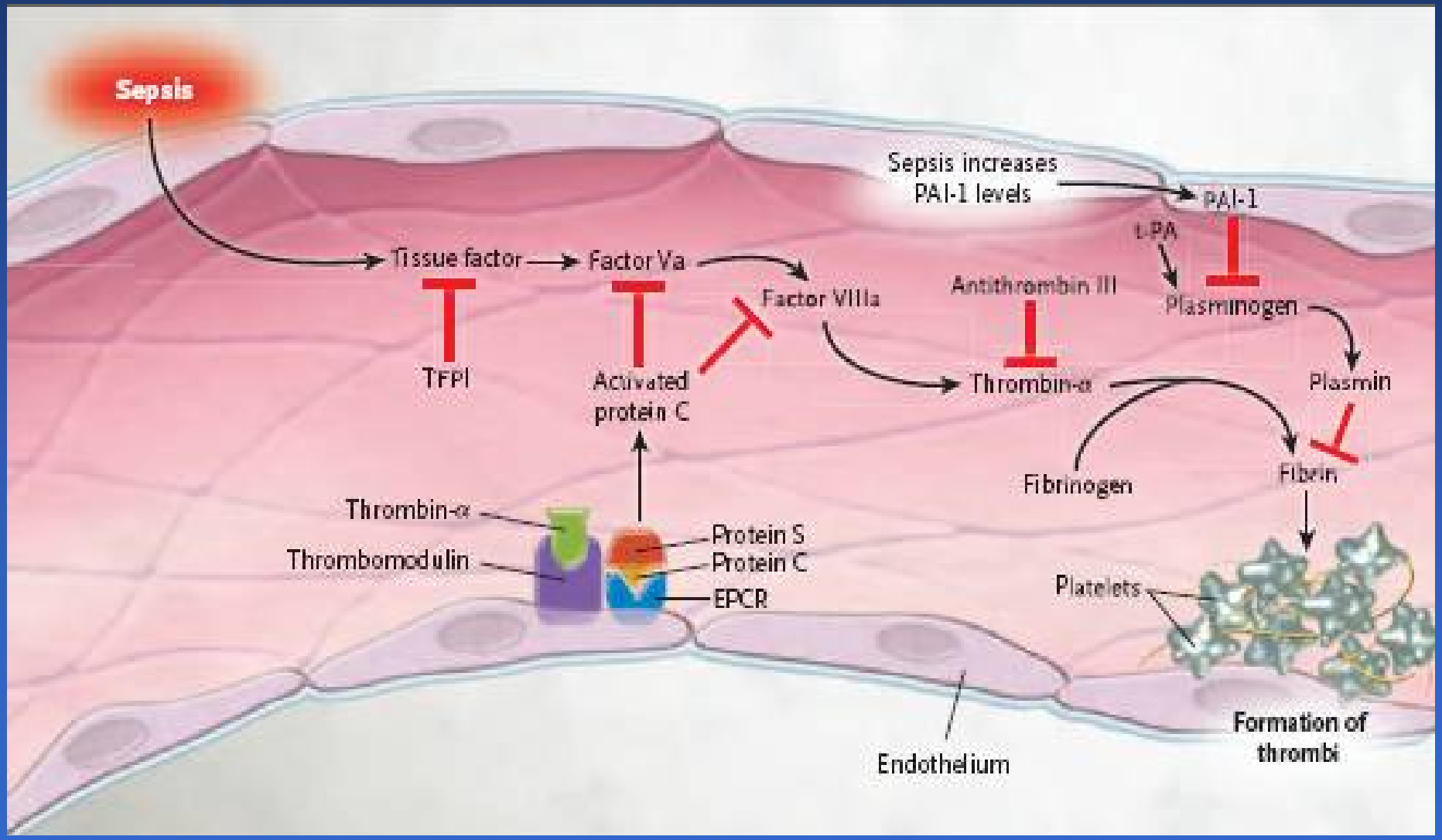
Clinical trials in sepsis……

…….The last five years….

Inflammatory cascade

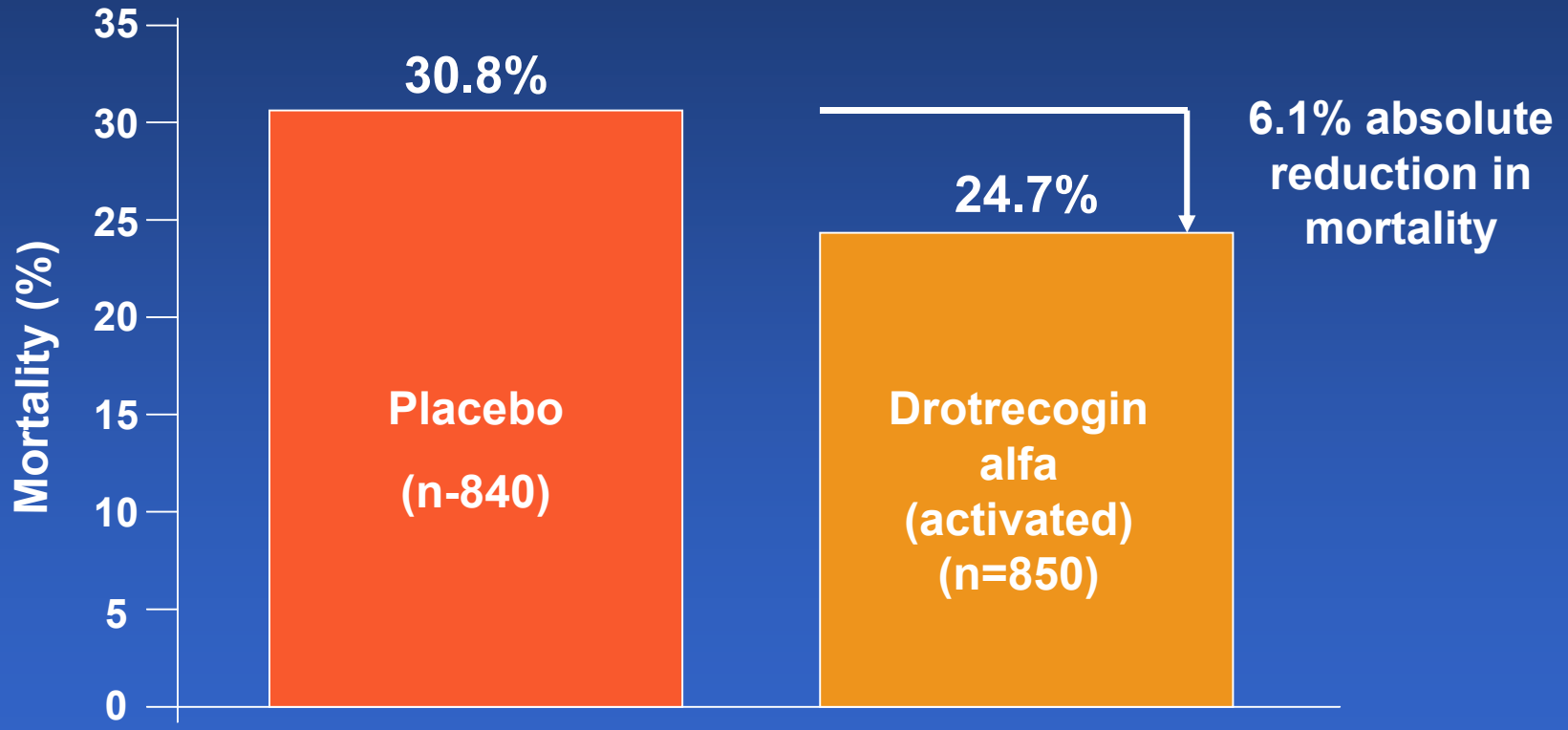


Coagulation cascade



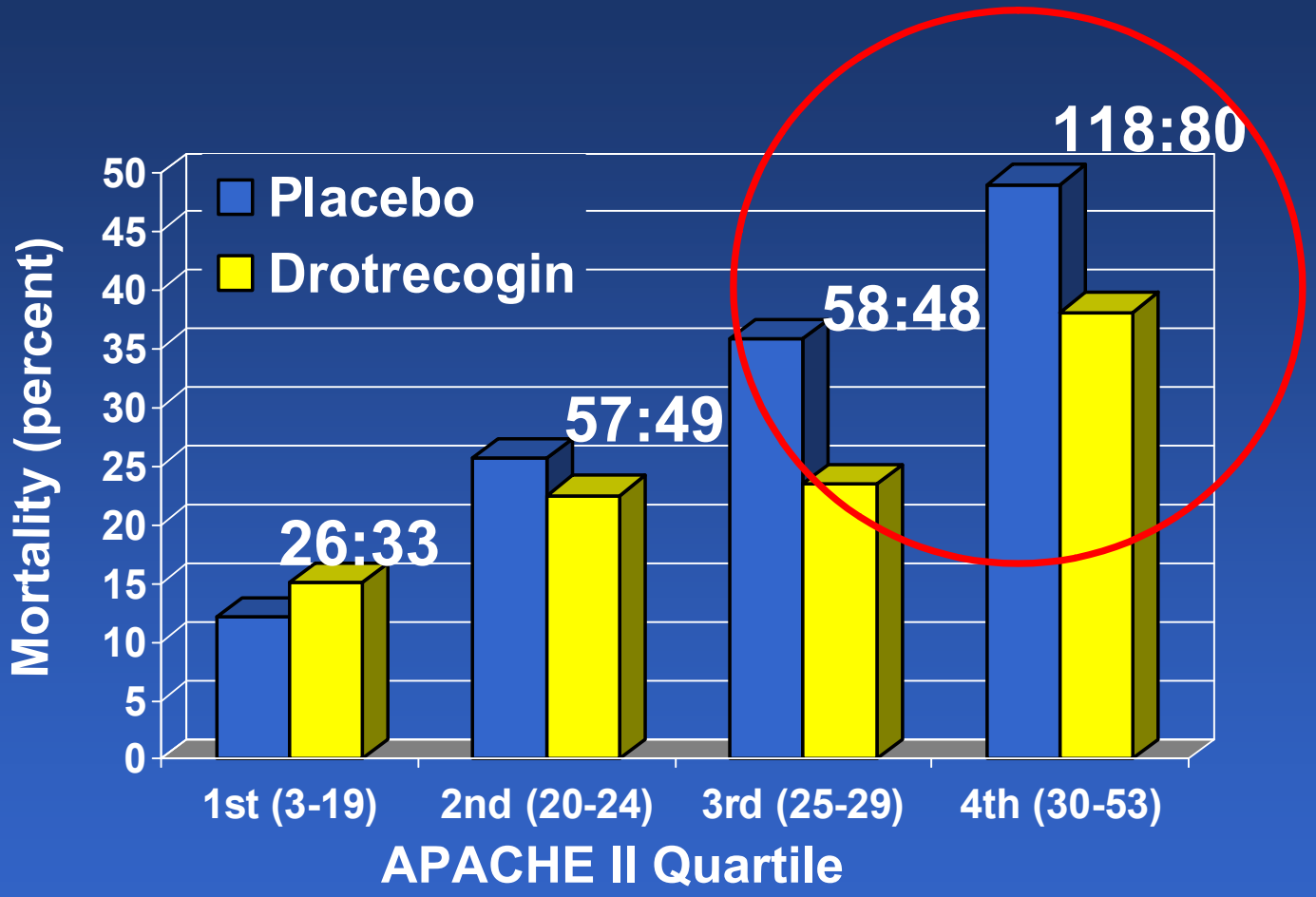
Results: 28-Day All-Cause Mortality

	Primary analysis results
2-sided p-value	0.005
Adjusted relative risk reduction	19.4%
Increase in odds of survival	38.1%



Bernard GR, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699-709

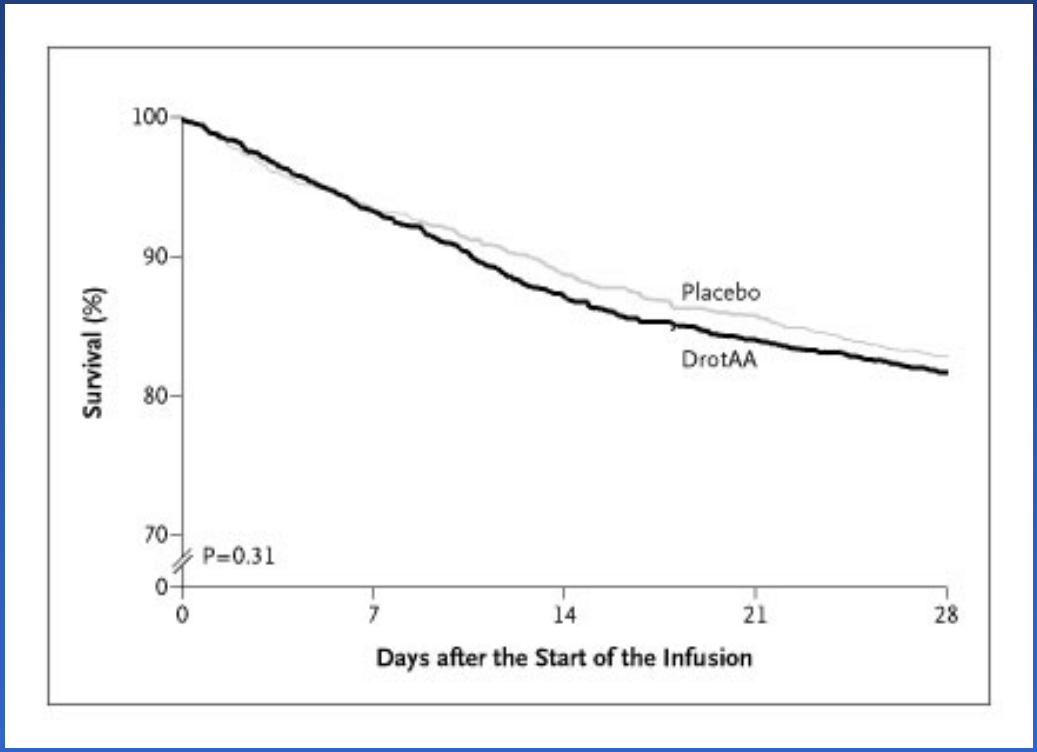
Mortality and APACHE II Quartile



*Numbers above bars indicate total deaths

Bernard GR. Drotrecogin alfa for the treatment of severe sepsis. Crit Care Med 2003; 31[Suppl.]:S85-S90

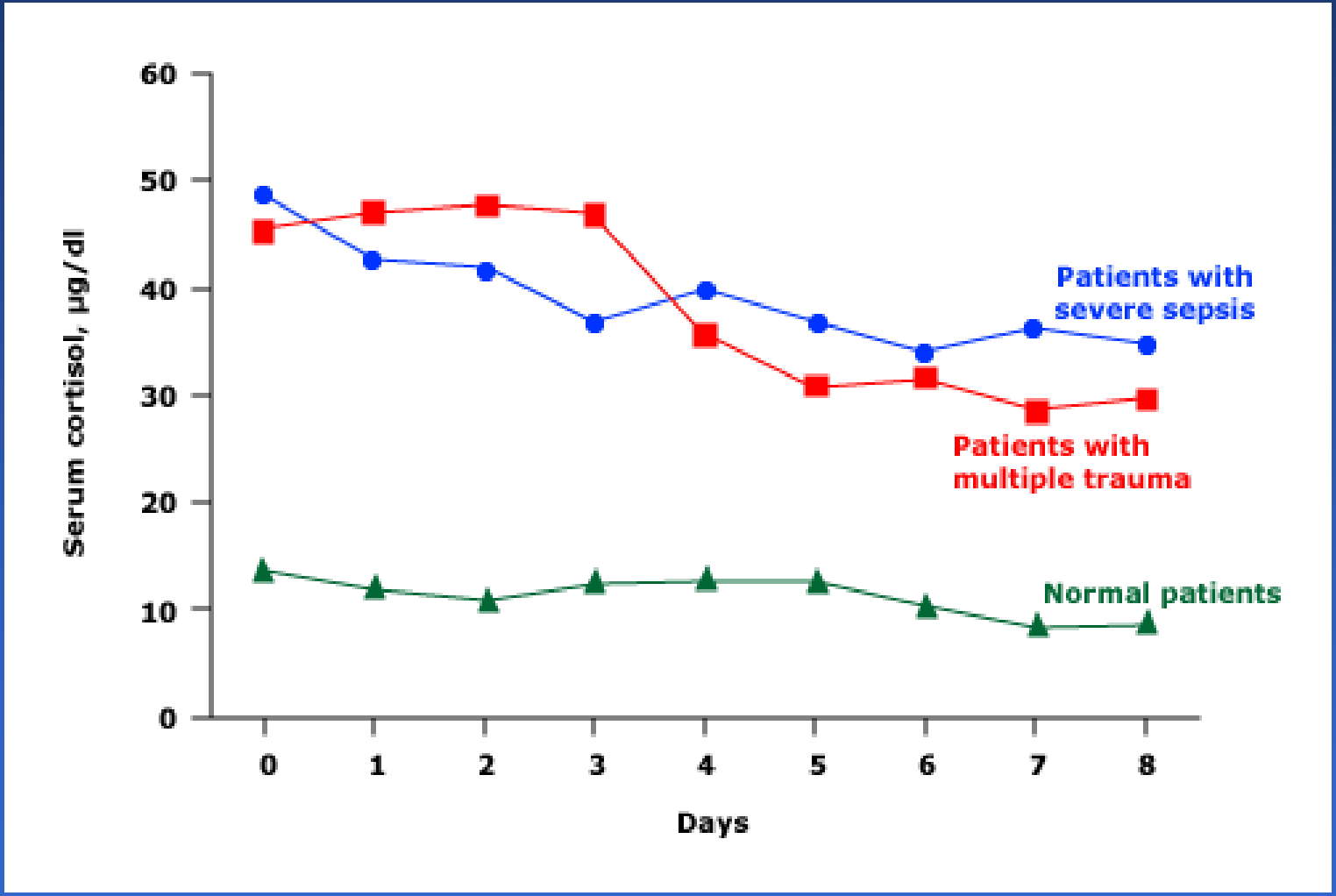
Drotrecogin alpha (activated) is not effective in adults with severe sepsis and a low risk of death*, and is associated with an increased rate of serious bleeding



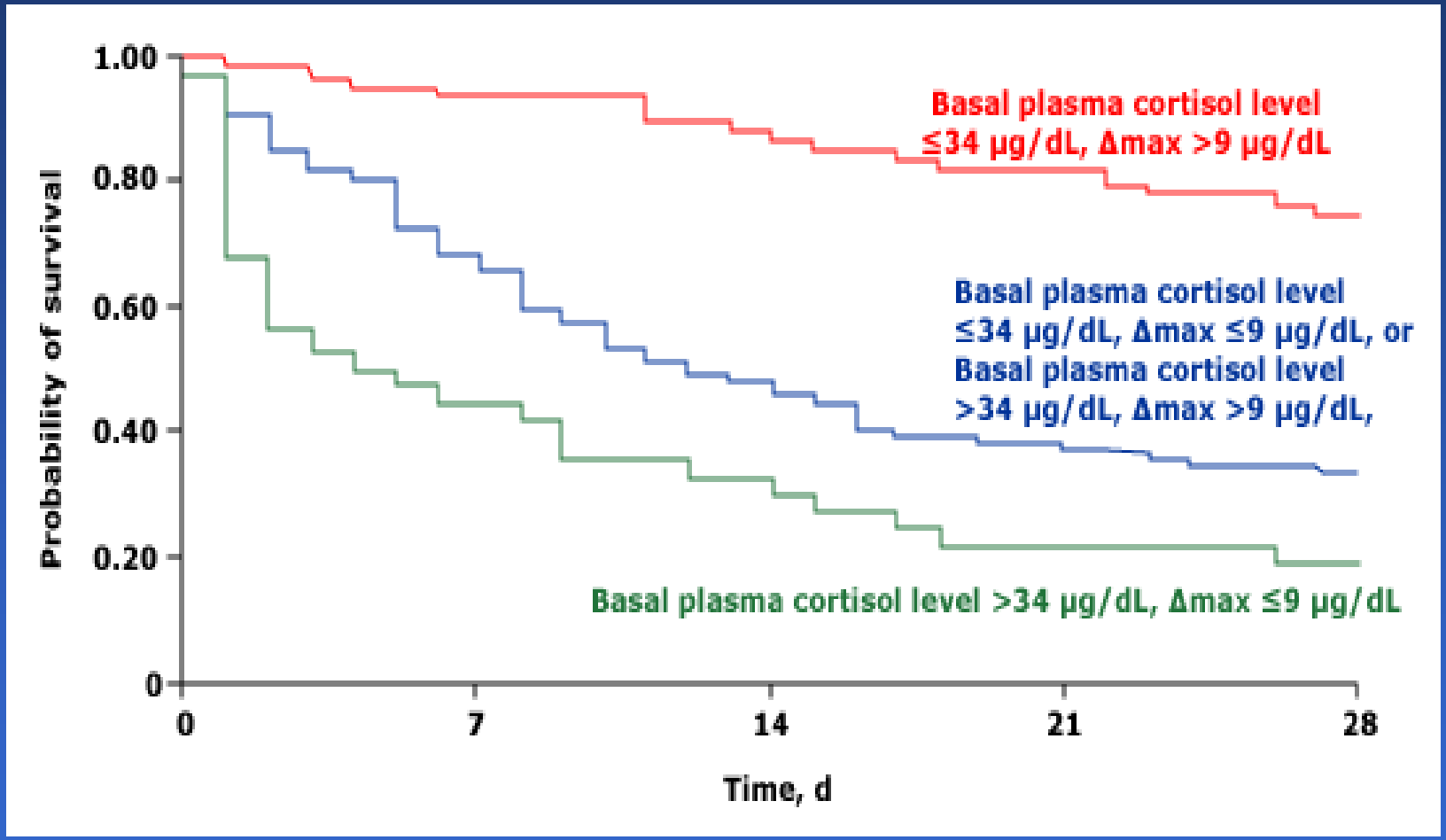
* APACHE II < 25 or Single organ failure

Abraham et al, NEJM 2005 353: 1332. ADDRESS trial group

Glucocorticoids in acutely ill patients

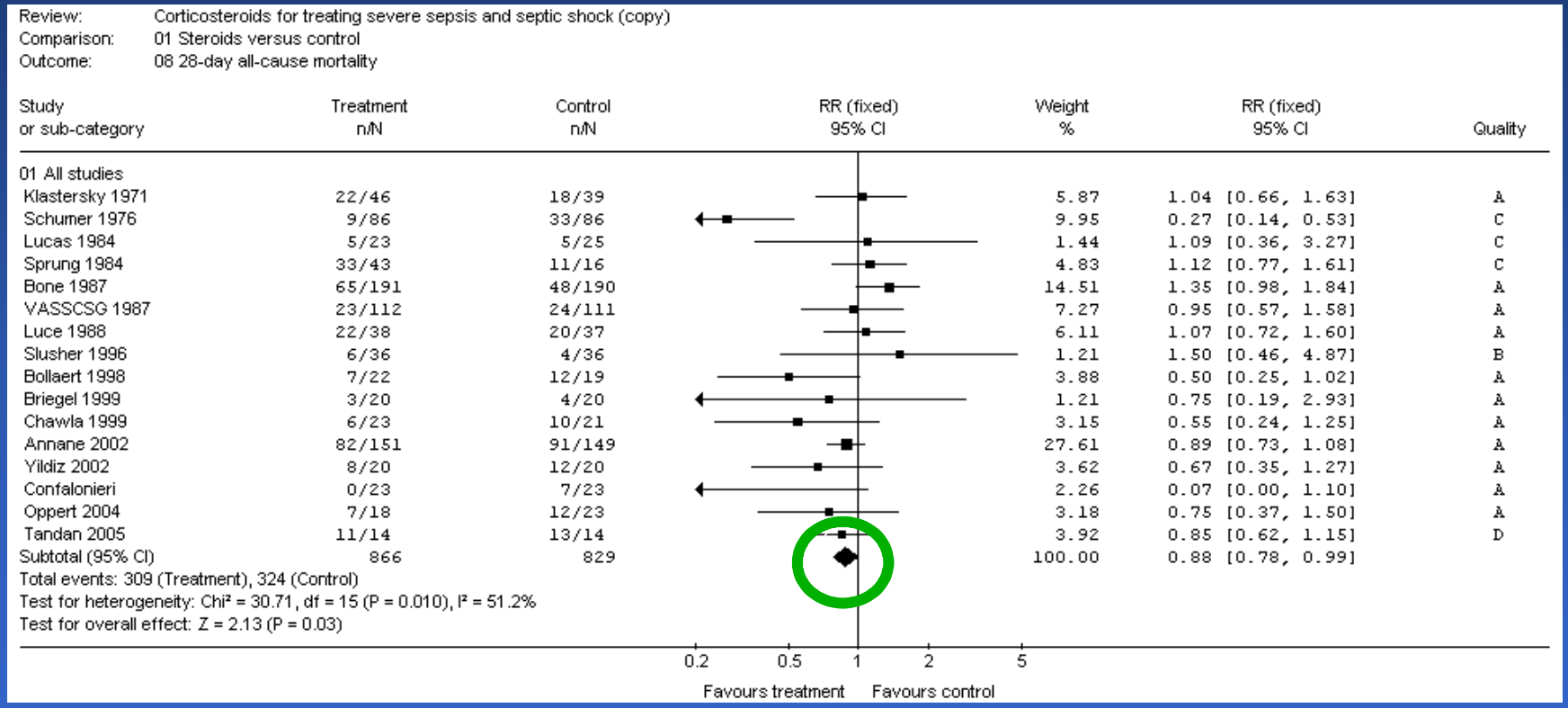


Adrenal responsiveness to 250 µg ACTH



Effect of steroids on 28 day mortality

RR 0.88 (0.78 to 0.99) p = 0.03

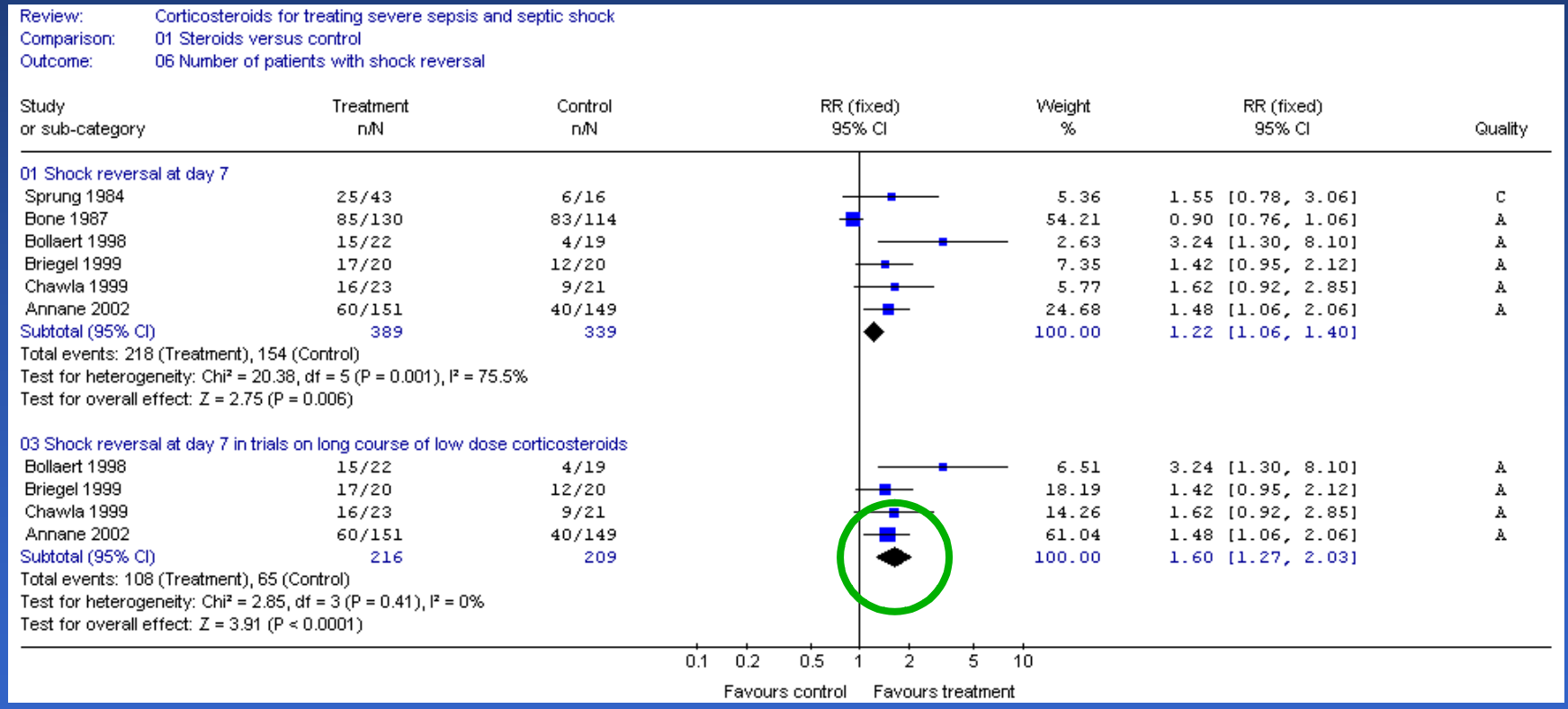


Favours treatment | Favours control

Annane et al, BMJ 2004 ***329****:480*

Effect of steroids on shock reversal

RR 1.6 (1.27 to 2.03) p < 0.0001



Favours control | Favours treatment

Annane et al, BMJ 2004 ***329****:480*

Controversies remain...

- Differences related to dosages
- Optimal definition of adrenal insufficiency
- Etomidate bolus depresses adrenal function
- No free cortisol routinely measured
- What about fludrocortisone?

In the meantime: probably useful to administer 200 mg hydrocortisone/day (for a maximum of 7 days) in vasopressor dependent septic shock

CORTICUS

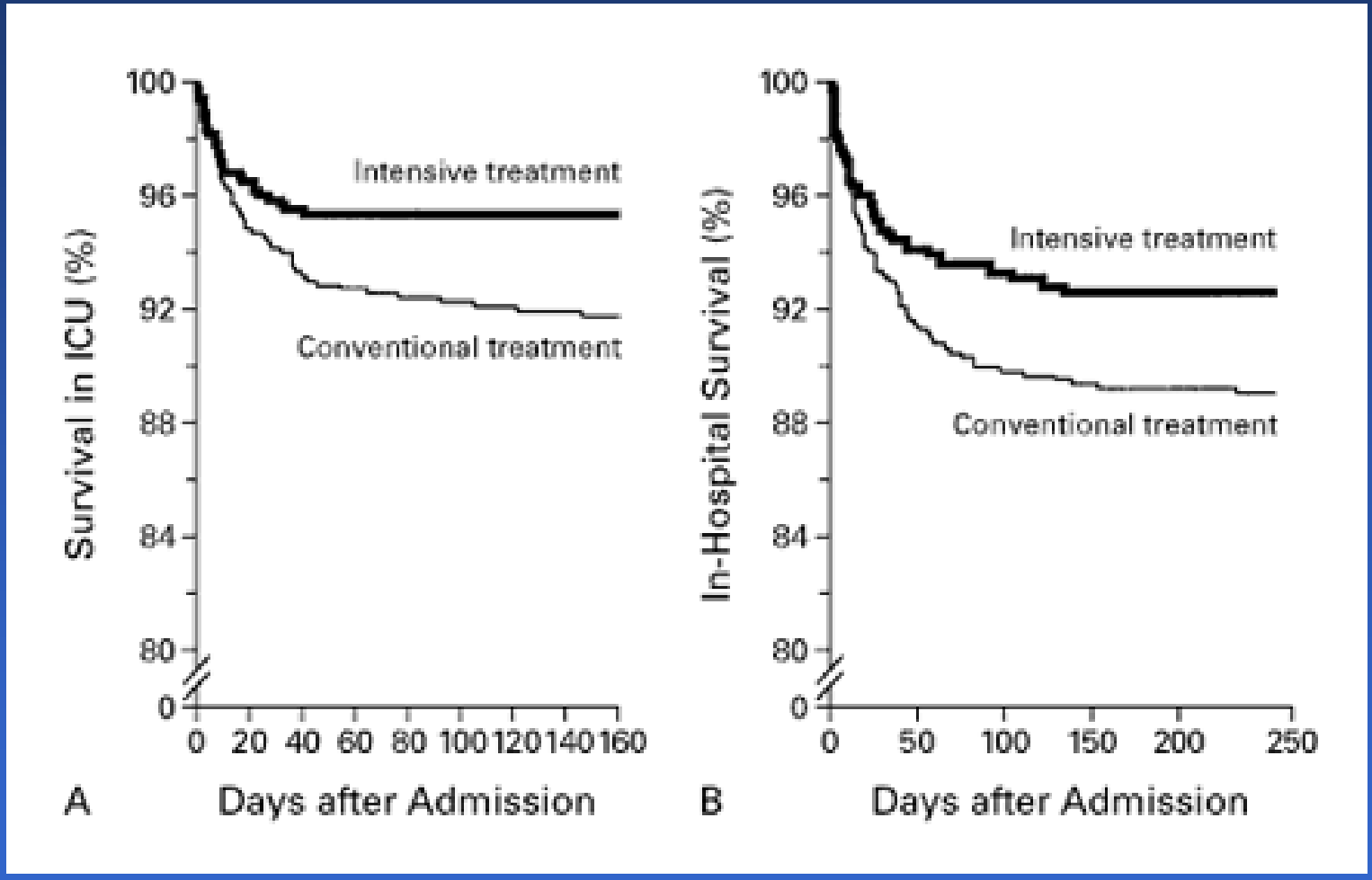
- International, prospective double-blind RCT of hydrocortisone in patients with moderate – severe septic shock
- HC 50 mg q6h for 5 d then tapering to d 11. No fludrocortisone.
- Primary EP 28 d mortality in nonresponders
- Approx 500 patients enrolled, study closed Nov 2005

CORTICUS - Results

- No effect on 28 day mortality in whole population or pre-identified subgroups
- Did not reverse shock in whole population or pre-identified subgroups
- ***Did*** reduce the time to shock reversal
- No significant problem with super-infection

Sprung et al., N Eng J Med 2007 (in press)

Intensive insulin therapy in critically ill patients



Van den Berghe G et al, NEJM 2001 345:1359

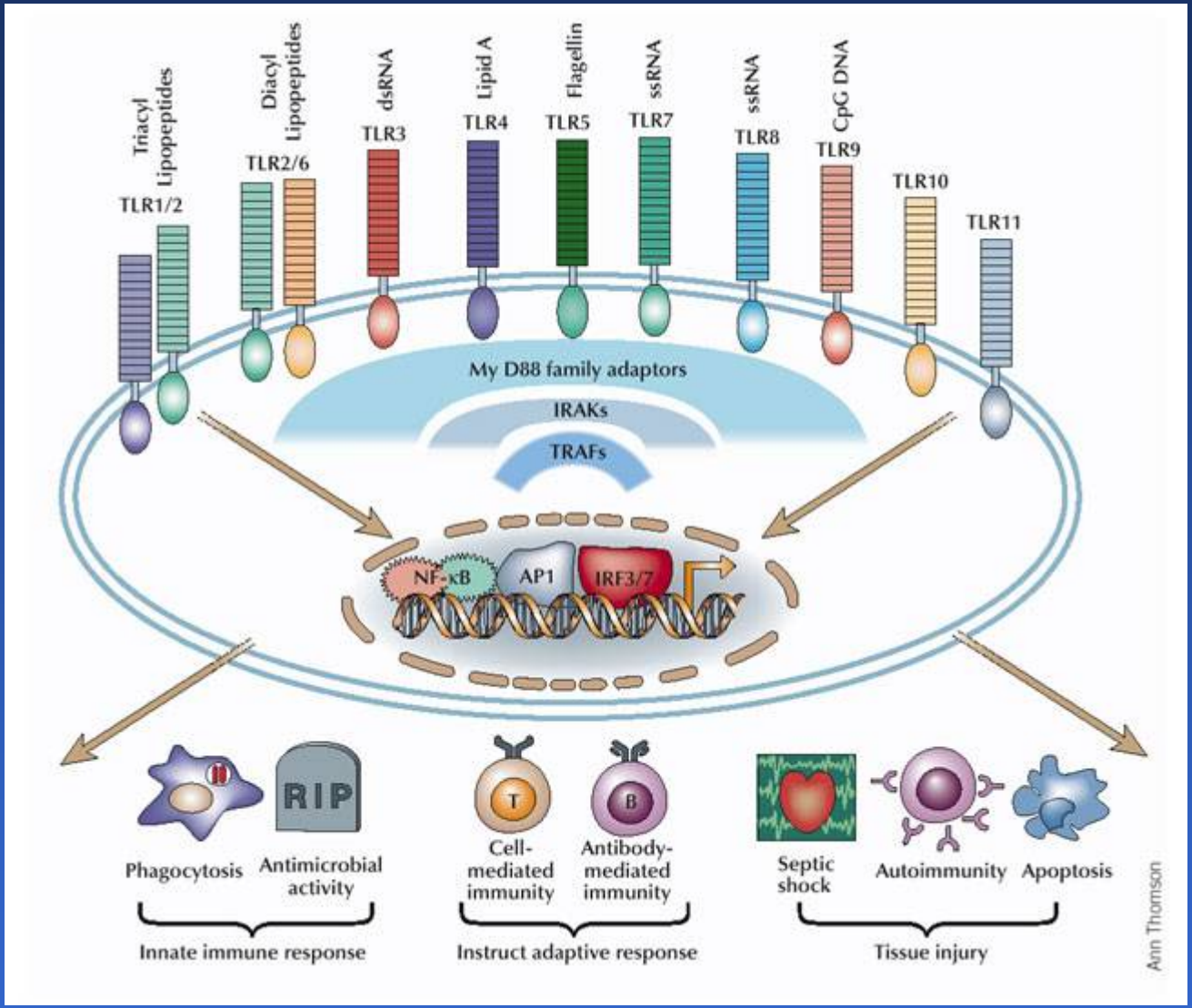
Intensive insulin therapy in medical patients on ICU for > 3 days

	ARR (%)	OR (95% CI)	P value
ICU mortality	38.1--- 31.3 Δ 6.8%	0.69 (0.50-0.95)	**0.02**
In hospital mortality	52.5 --- 43.0 Δ 9.5%	0.63 (0.46-0.89)	**0.003**

OR and p value corrected for type & severity of illness

*Van den Berghe G et al, N Engl J Med 2006 **354**:449*

Yet more clinical trials in sepsis……

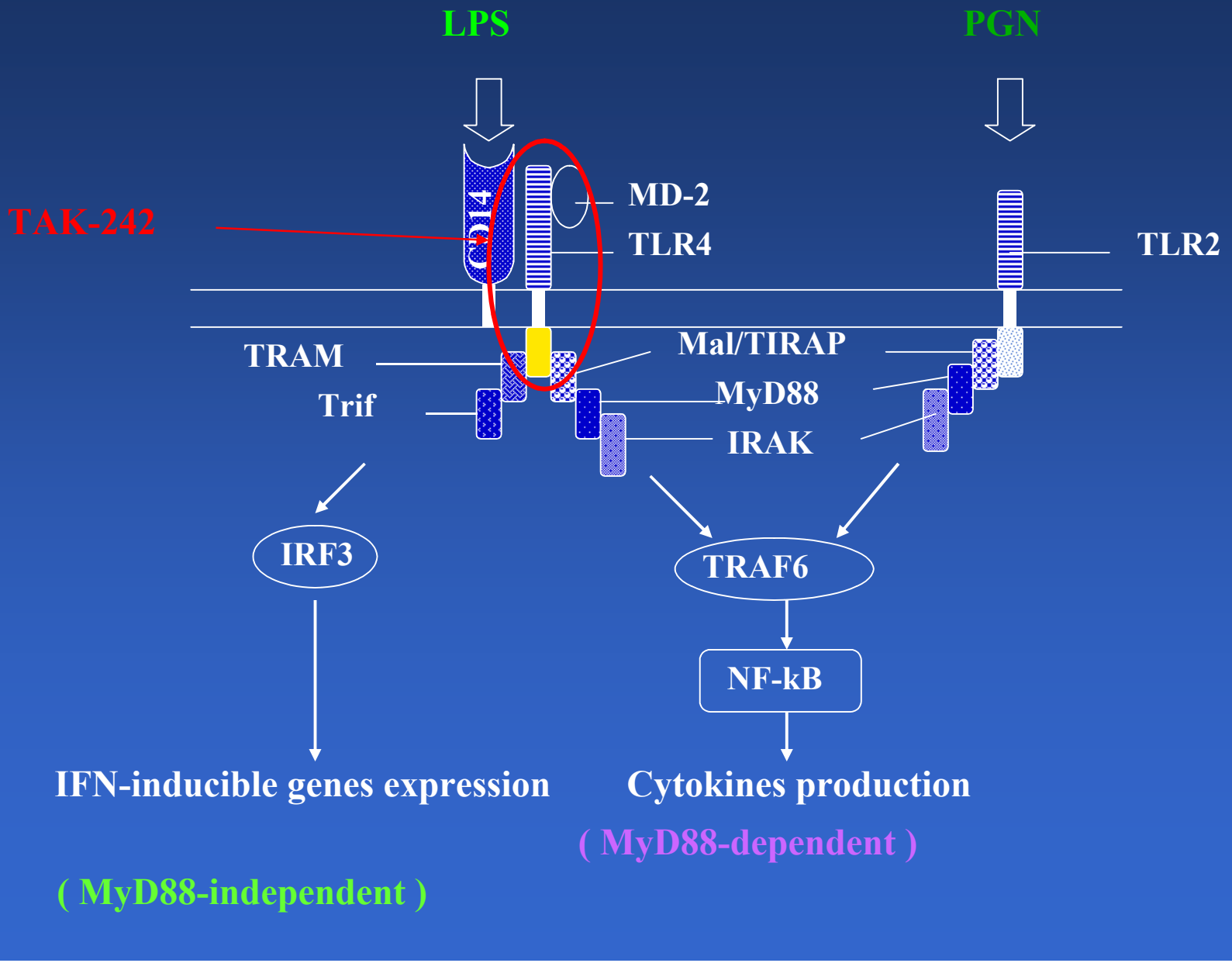


Modlin & Cheng, Nature Med 2004 10:1173

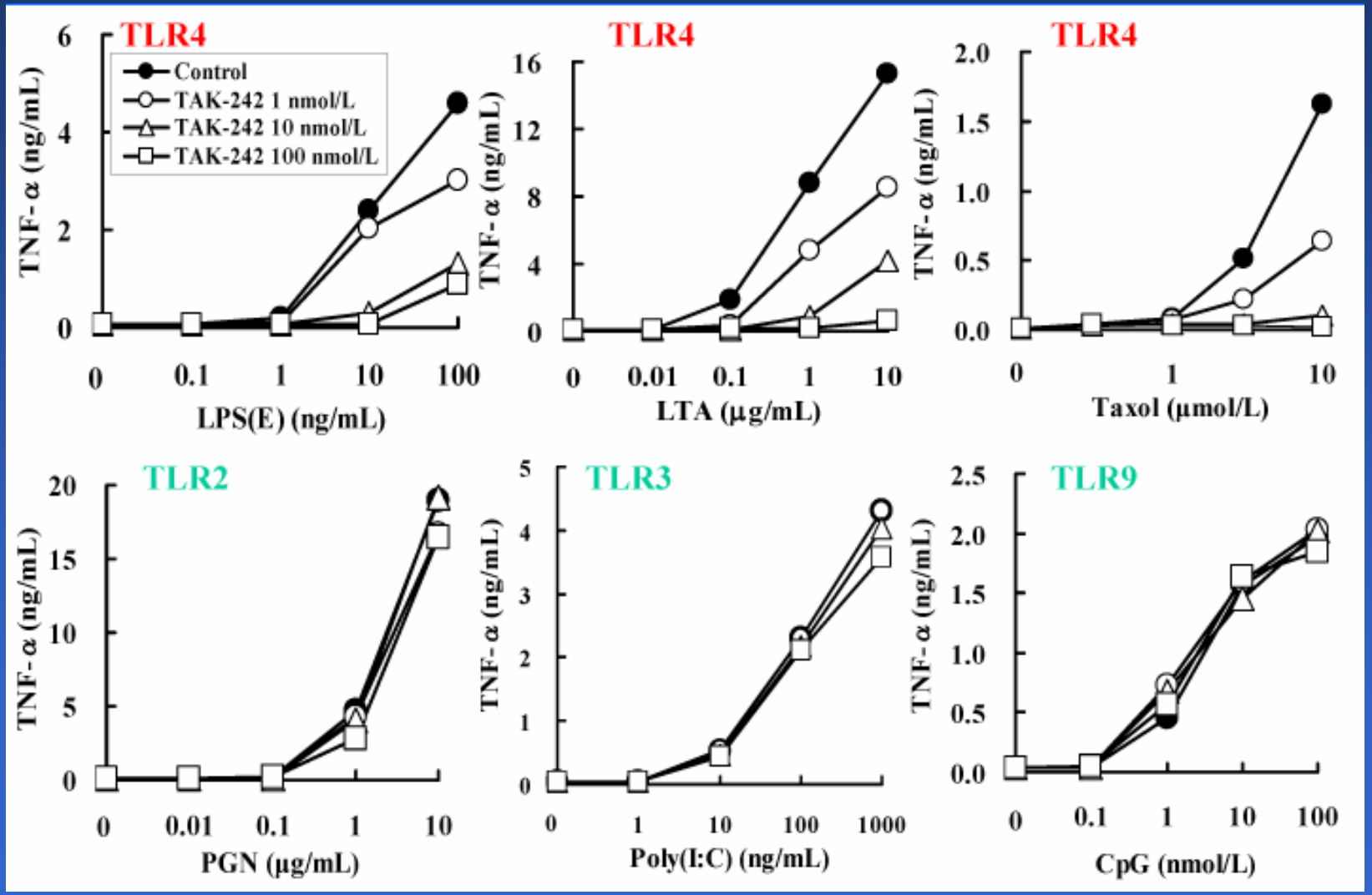
TAK-242

- Novel small molecule signal transduction inhibitor
- Effective when given up to 4 h after LPS challenge in mice
- Phase I human studies confirm broad inhibition of cytokines
- Excellent safety profile

Putative target site of TAK-242



TAK-242 exhibits a TLR4-specific mode of action

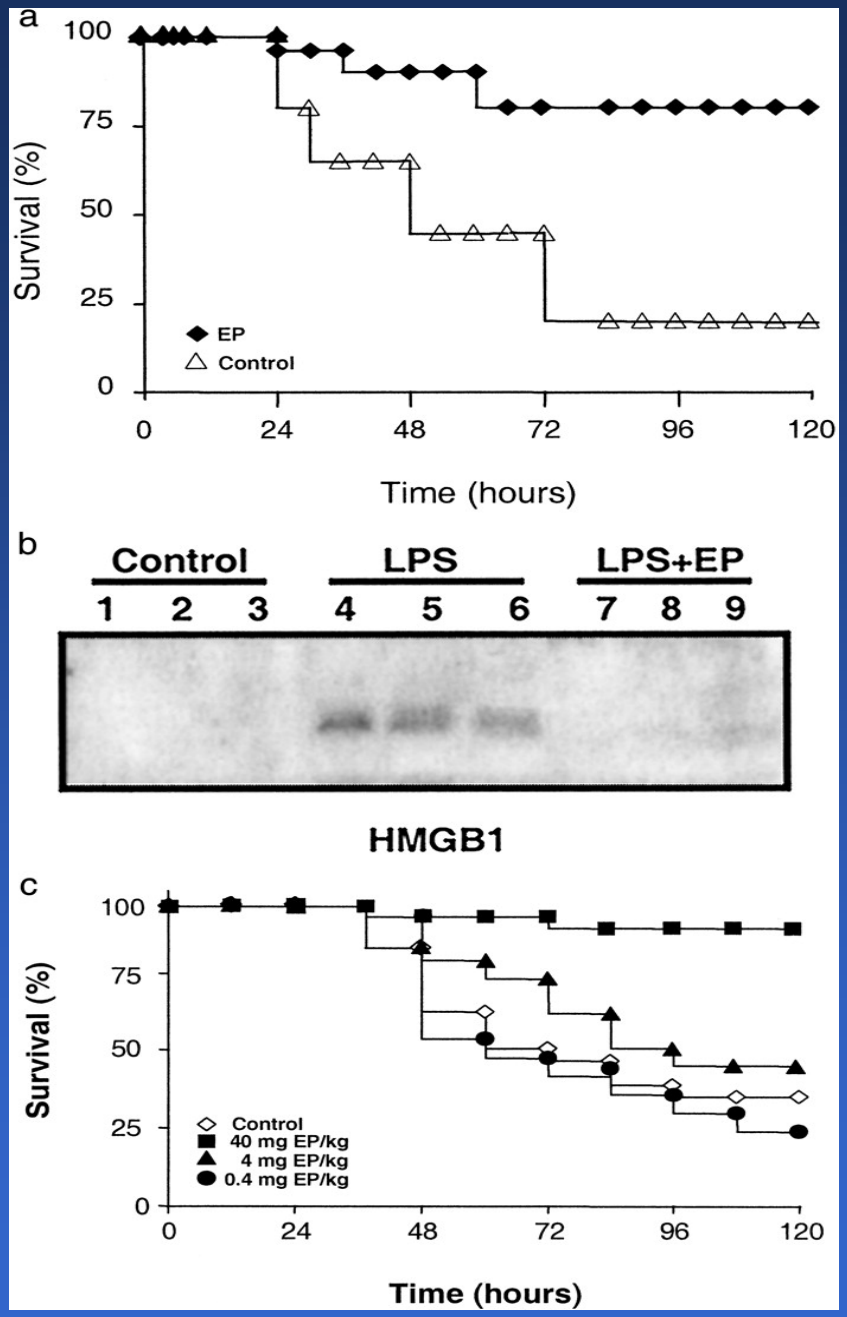


Phase II study of Eritoran (E5564) in sepsis

N = 293	28 d mortality (%)	RRR (%)	p
Placebo	33.3		
Low dose	32.0		
High dose	26.9	6.4	0.34

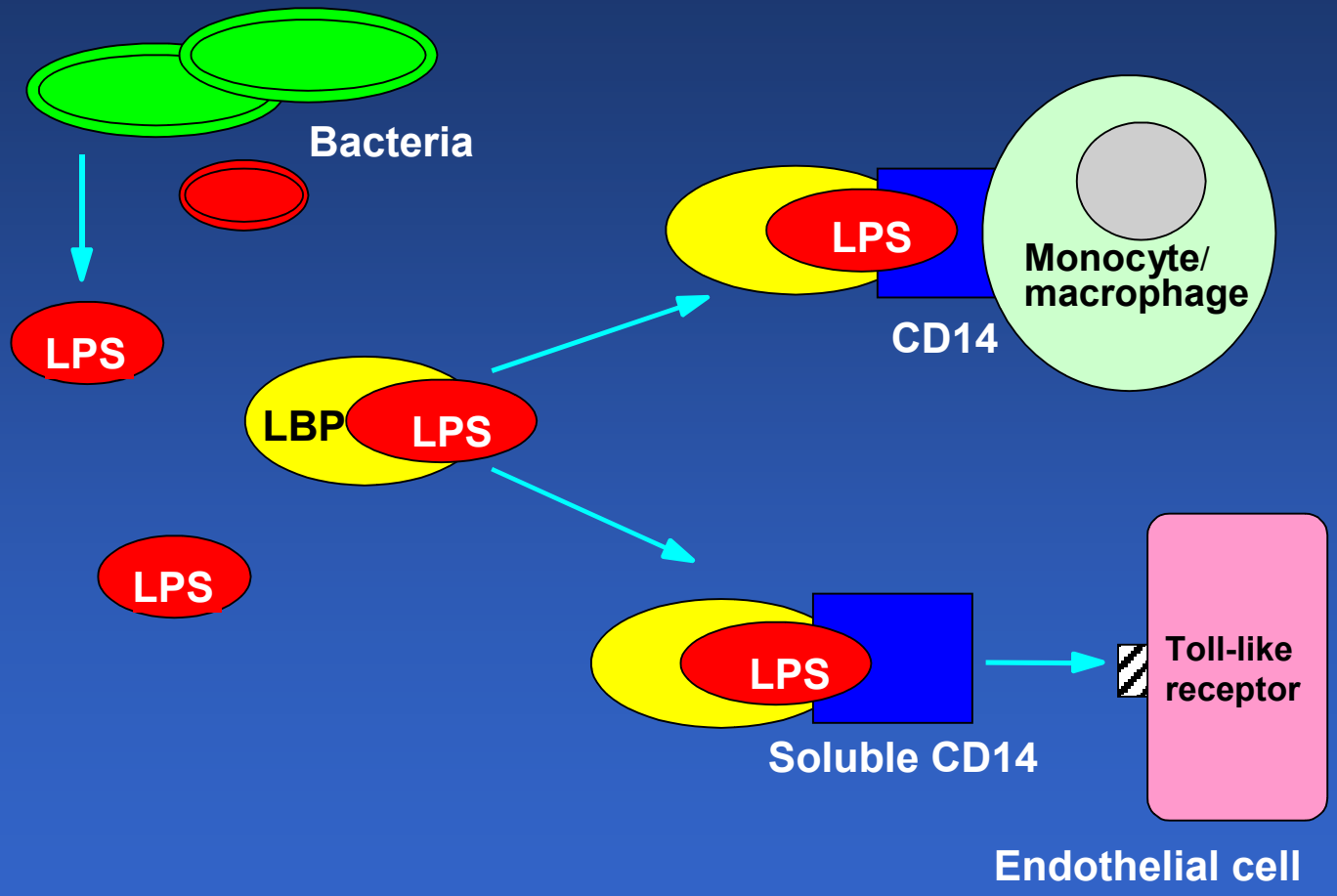
Eisai, press release, Aug 2005

Ethyl pyruvate prevents lethal CLP sepsis in mice by reducing HMG-B1

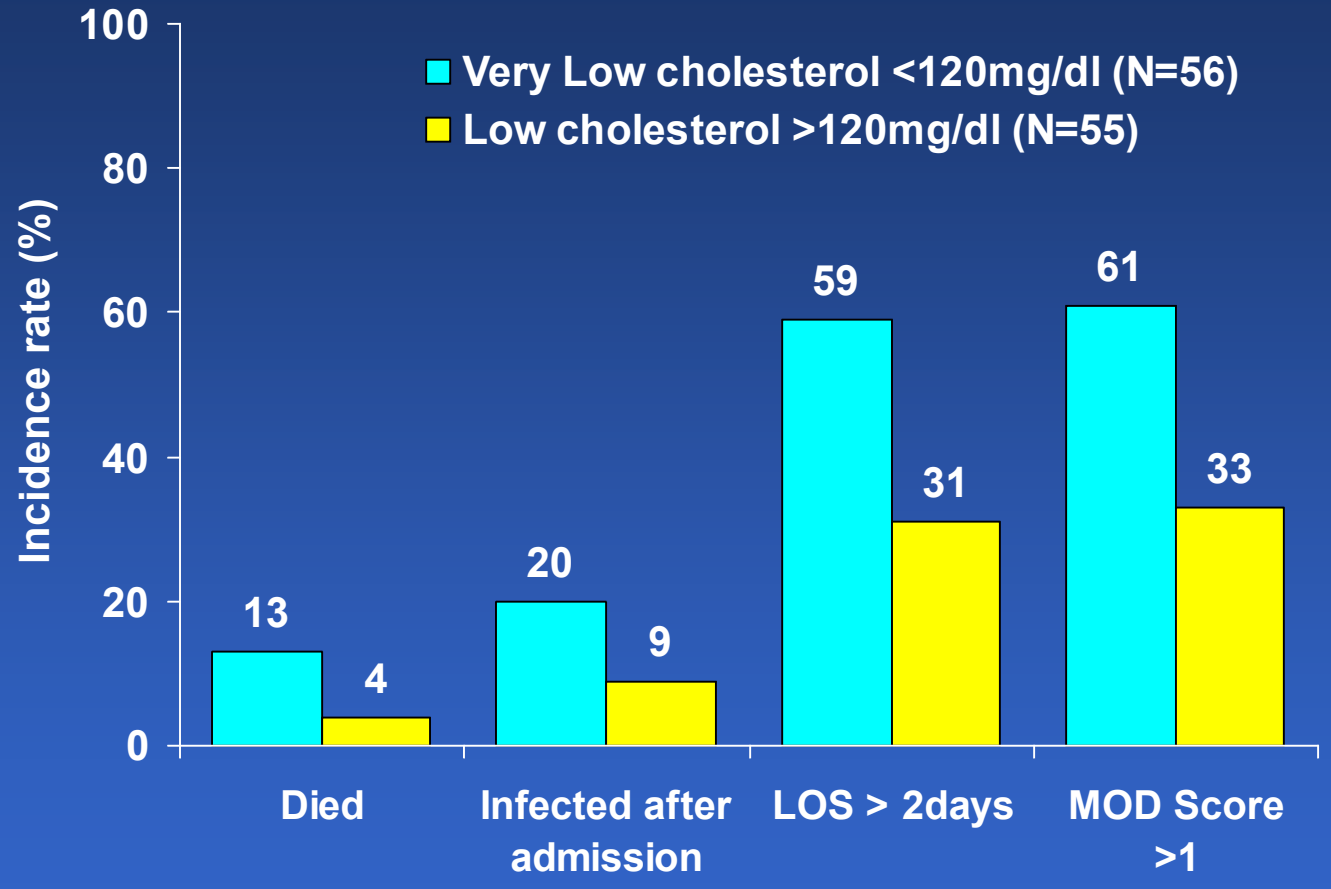


Ulloa et al, PNAS 2002; 99:12351

The interaction of endotoxin (LPS) with host cells



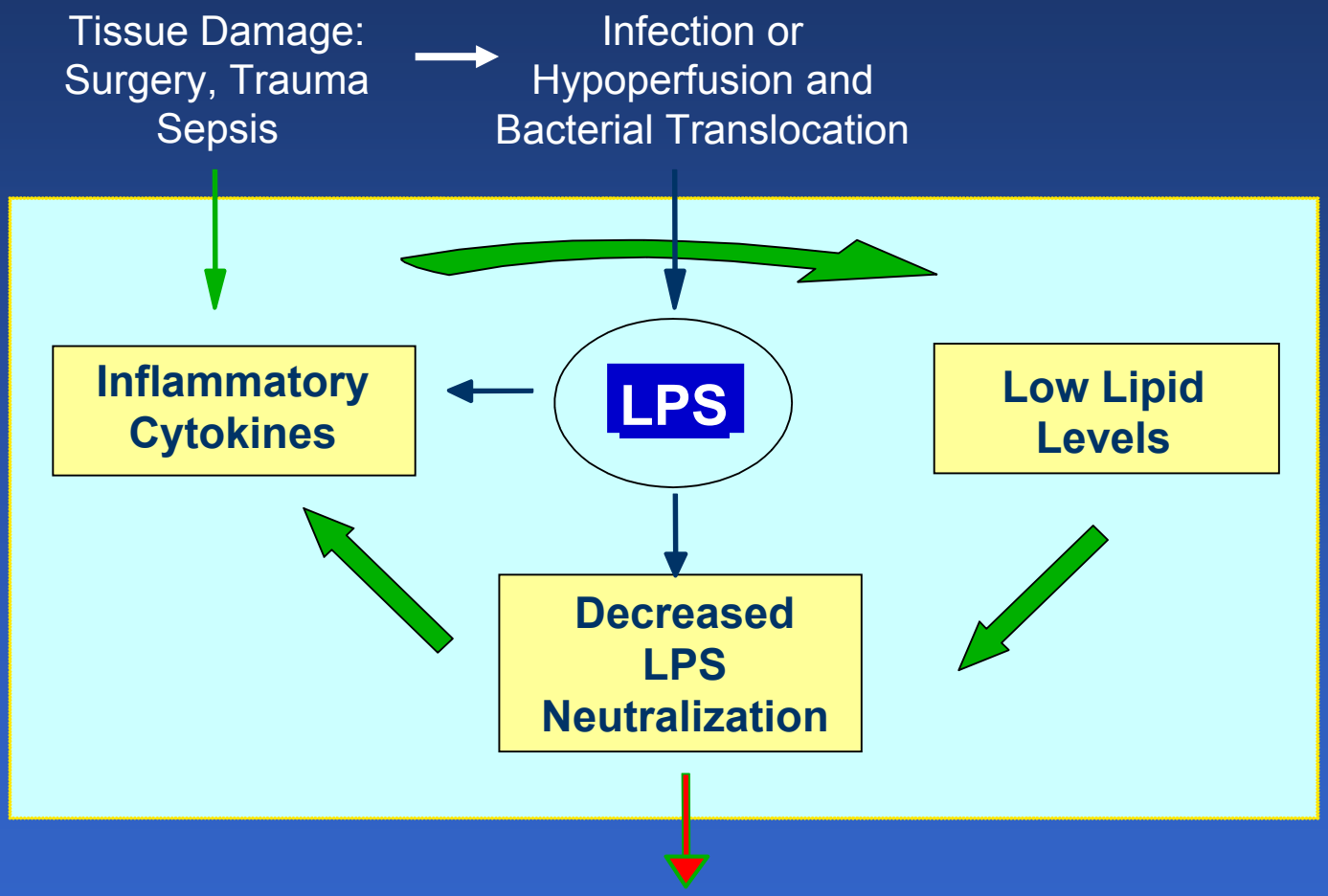
Total cholesterol concentration and outcome in 111 ICU patients



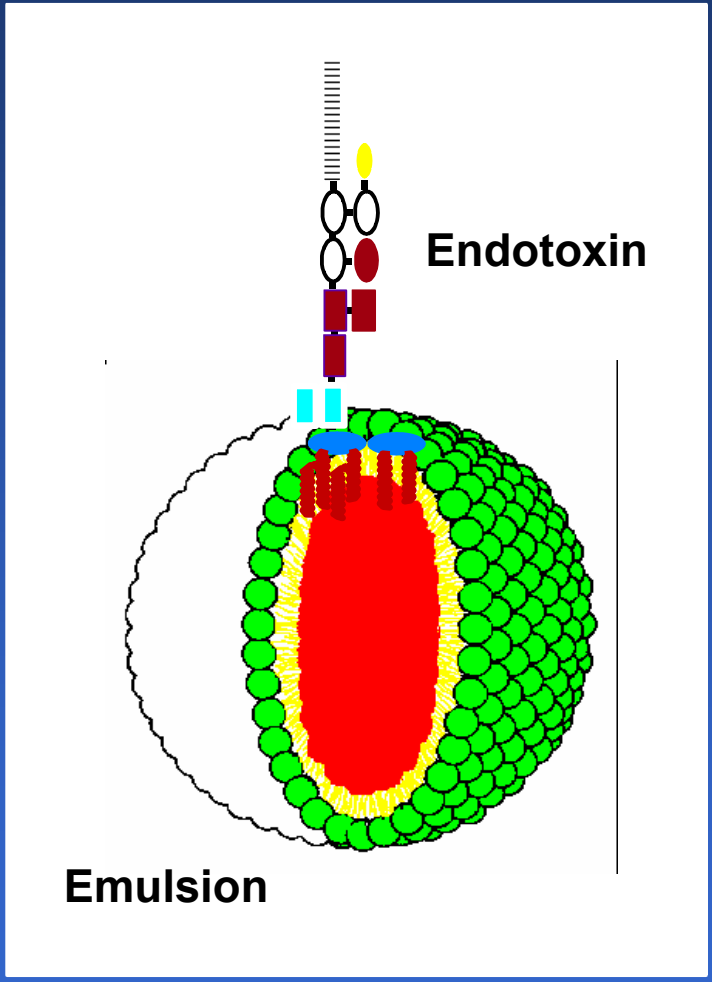
LOS = Length of ICU Stay
MOD = Multiple Organ Dysfunction

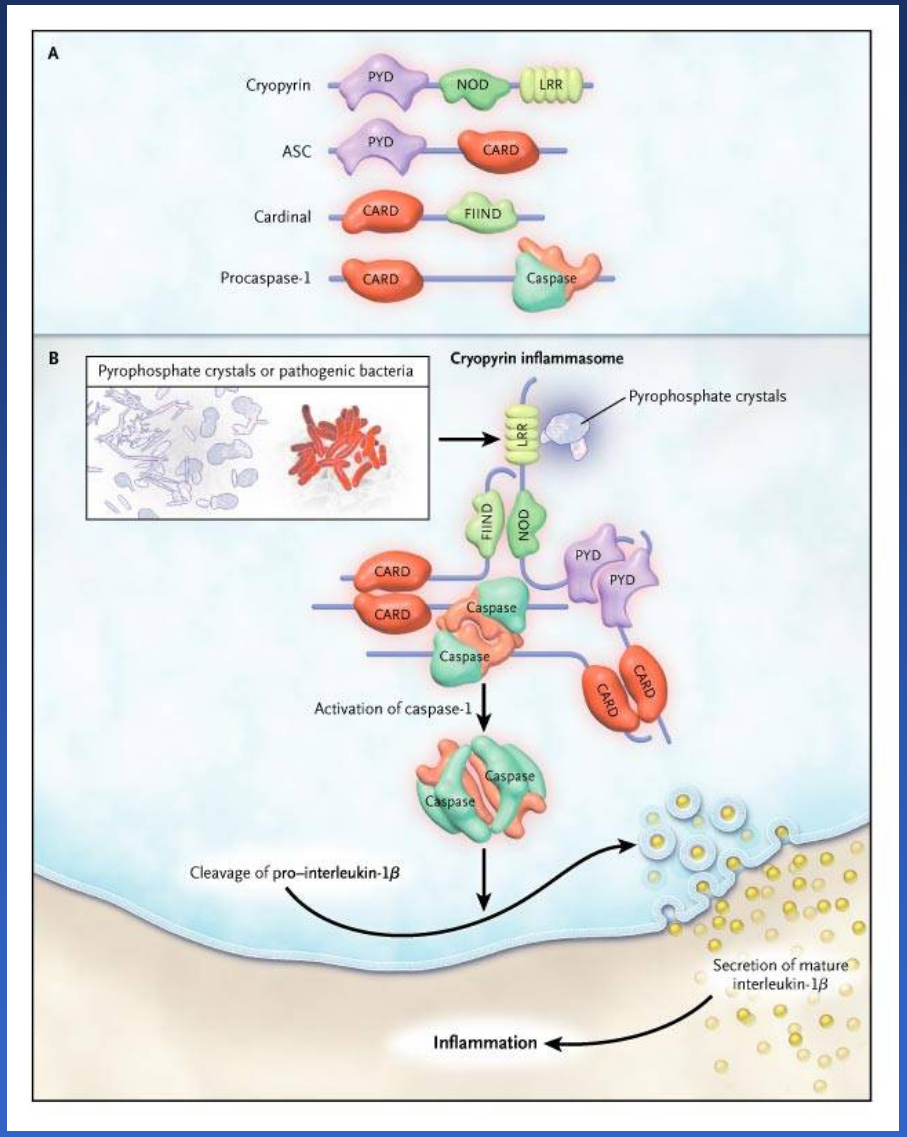
Gordon et al. Crit Care Med.

Hypothesis: linking lipid levels, cytokines, and clinical outcome



GR270773 Lipid Emulsion





"Inflammasomes catapult cryopyrin from involvement in a rather obscure group of disorders into the realm of common bacterial infections"

Drenth J and van der Meer J. N Engl J Med 2006;355:730-732

The NEW ENGLAND JOURNAL of MEDICINE

A role for statins in sepsis?

- Pleiotropic anti-inflammatory effects
- Prevent lethal sepsis in mice used either as prophylaxis or therapy

  (Merx, Circulation 2005 112:117)
- Beneficial in human LPS-challenge model

  (Steiner, Circulation 2005 111:1841)
- Clinical observational studies suggest statins reduce risk of complications/death in pts admitted with sepsis

  (Almog, Circulation 2004 110:880)

  (Kruger, Intensive Care Med 2006 32:75)
- Statins reduce the risk of developing sepsis after cardio-vascular event

  (Hackam, Lancet 2006 367:413)

Statins do not protect against CAP

An example of the "healthy user" effect?

Univariate analysis n = 3415	Statin use YES	NO	OR	p
Death (%)	8	10	0.75	0.18
ICU admission (%)	9	10	0.84	0.39
Death or ICU Admission (%)	15	19	0.8	0.15
Multivariate analysis				
Death or ICU Admission (%)			1.1	0.61

Majumdar et al, BMJ 2006 333:999

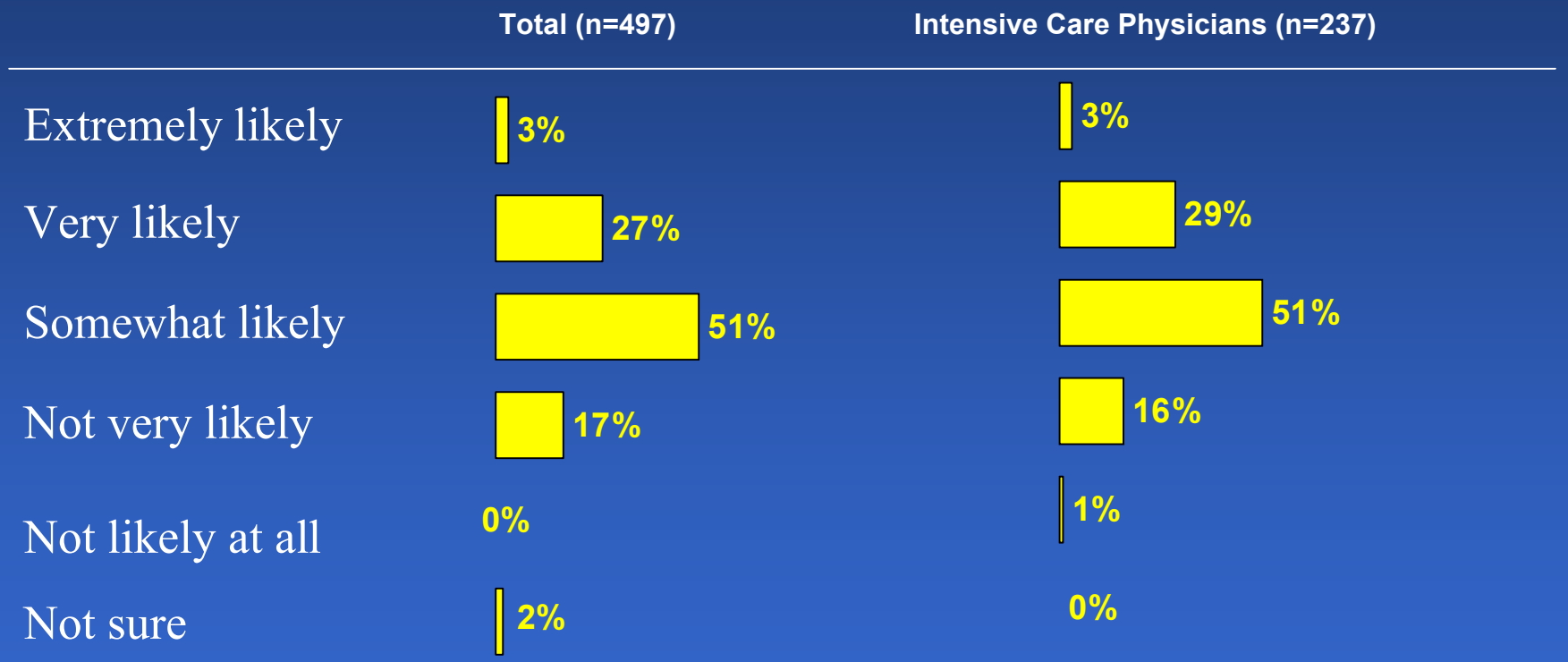
So what's going on here?

The 1992 ACCP/SCCM Consensus definitions for Sepsis and Organ Failure

- Infection: microbial phenomenon characterised by an inflammatory response to the presence of micro organisms or the invasion of normally sterile host tissue by these organisms.
- Sepsis: systemic response to infection manifested by ≥ 2 of:
  - Temp > 38^{o}C or < 36^{o}C
  - HR > 90 bpm
  - RR > 20 bpm or $PaCO_2$ < 32 mmHg
  - WBC > 12 x 10^9/L, < 4 x 10^9/L or >10% band forms

Bone et al, Chest 1992 101:1644

Because there is no common definition for sepsis, how likely is it that the diagnosis of sepsis is being missed? Is it...



Ramsay, Crit Care 2004 8:R409.

*Systemic host responses in **Severe Sepsis** analyzed by causative microorganism and treatment effects of drotrecogin alfa*
Opal et al; Clin Infect Dis 2003 37:50-8

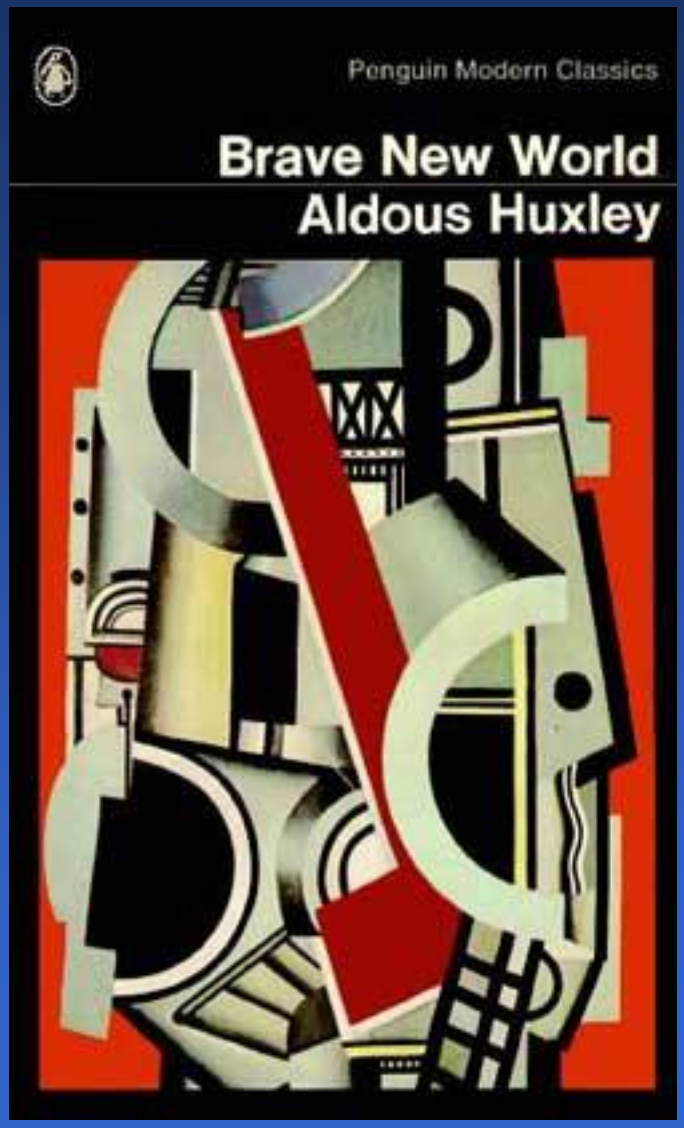
"Eligible patients had known or suspected infections, …had ≥ 3 signs of systemic inflammation, and had ≥ 1 sepsis-associated acute organ dysfunction"

*Glucocorticoid insufficiency in patients who present to the hospital with **Severe Sepsis:** a prospective clinical trial*
Manglik et al, Crit Care Med 2003 31:1668-75

"Severe sepsis was defined as sepsis with organ dysfunction, inadequate perfusion, or hypotension. Abnormalities could include, but were not limited to, lactic acidosis, oliguria, and/or acute mental status.

INDICATIONS AND USAGE Xigris is indicated for the reduction of mortality in adult patients with **severe sepsis** (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II, *see* **CLINICAL STUDIES**). Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

Xigris™ product label, FDA website



2001 SCCM/ESICM/ACCP ATS/SIS International Sepsis Definitions Conference

Levy MM et al, Crit Care Med 2003 31:1250 - 1256

2001 SCCM/ESICM/ACCPATS/SIS International Sepsis Definitions Conference

Diagnostic criteria for sepsis (selected)

- Infection, & some of the following:
- Temp > 38.3 or < 36
- HR > 90
- Tachypnea
- Altered mental status
- Pos fluid balance
- Hyperglycaemia
- WBC > 12 $x10^9$/L,<4 $x10^9$/L
- CRP or PCT > 2 SD
- Hypotension
- Hypoxaemia
- Acute oliguria
- Raised creatinine
- Coagulopathy
- Ileus

Putative markers of sepsis

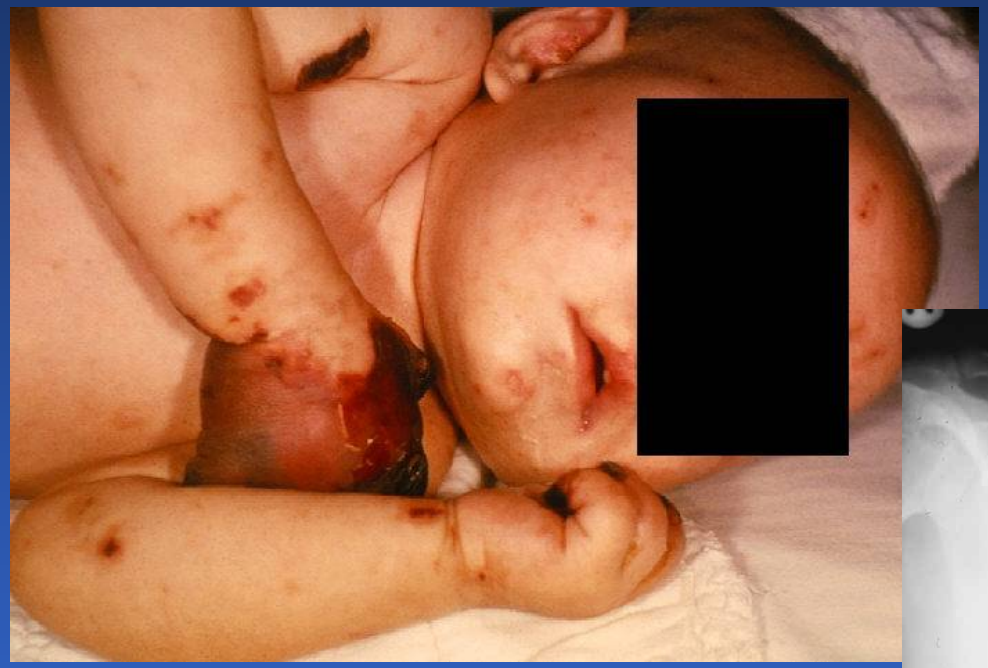
- Microbial products
  - LPS; Bacterial DNA
- Physiological
  - T; HR; RR; CI; Urine
- Cell surface markers
  - CD40; CD11b; CD64
- Soluble receptors
  - IL-2R; sELAM-1; sTNFR; sCD14 etc
- Cytokines
  - IL-1; Il-1ra; IL-6; IL-8; IL-10; TNF; HMG-1 etc
- Acute phase proteins
  - CRP; LBP; Fibrinogen
- Coagulation factors
  - FDPs; PAI-1; TPA etc
- Various
  - PCT; Lactate; Elastase etc

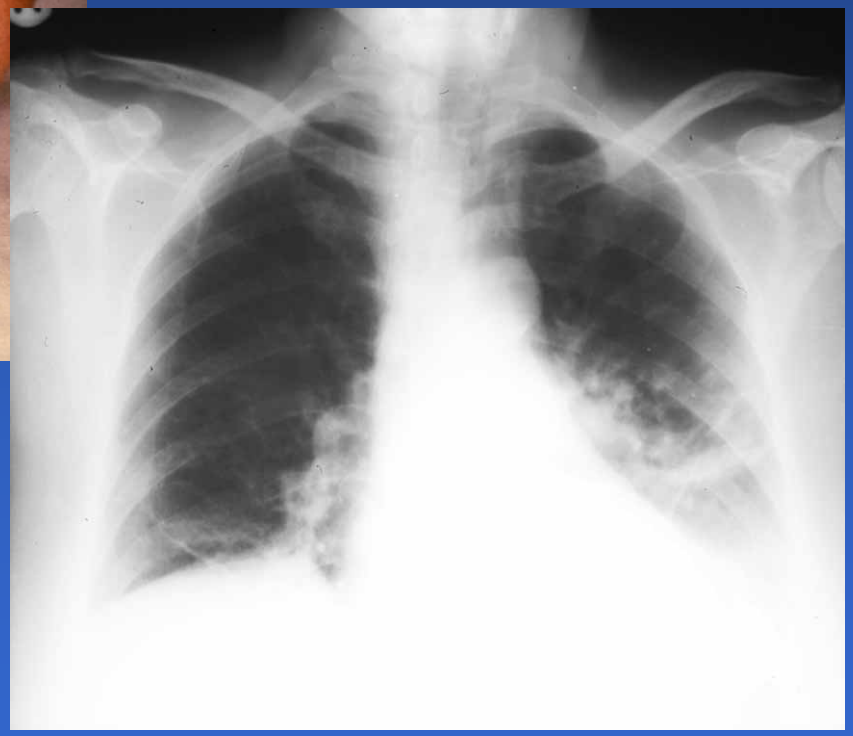
Can we do better? The elusive marker of sepsis

"More than 80 putative markers of sepsis have been described. All correlate with mortality (but none are useful) in stratifying patients with respect to diagnosis or response to therapy. Their limitations arise from the challenges of establishing causality in a complex process like sepsis, and of stratifying patients into more homogeneous populations".

Measures, markers and mediators: Towards a staging system for clinical sepsis. A Report of the 5th Toronto Round Table. Marshall JC et al, Crit Care Med 2003 31:1560

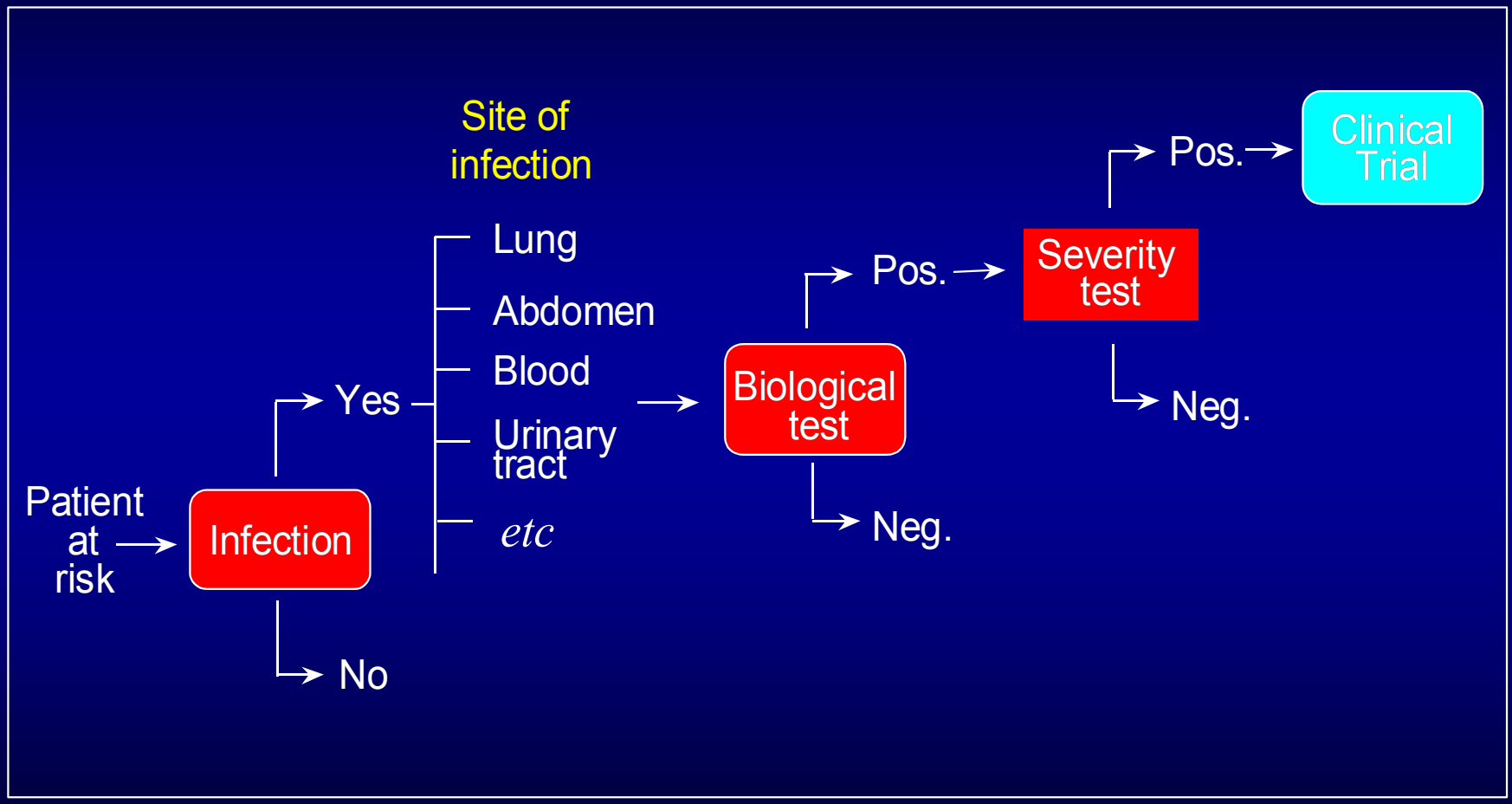
Is this disease…..





really the same as this disease?

Figure 2



Cohen et al, Crit Care Med 2001 29:880-886

Some provocative conclusions..

- Sepsis is an important clinical syndrome that is associated with a significant morbidity and mortality, but…..
- We can't define it
- We can't agree how to recognise it at the bedside
- We can't agree on a test(s) to detect it

So what should we do….?

- Retain “sepsis” as a clinical term but abandon the idea of developing a single “anti-sepsis” drug
- Focus instead on specific infectious diseases
- Continue to explore pathophysiology to identify new targets, but for defined settings
- Go for incremental improvement rather than the big bang – the cancer model