Best of Brussels - 2012

International Symposium on Intensive Care and Emergency Medicine

March 20 - 23, 2012

BELGIUM - Brussels -Congress Center (SQUARE)

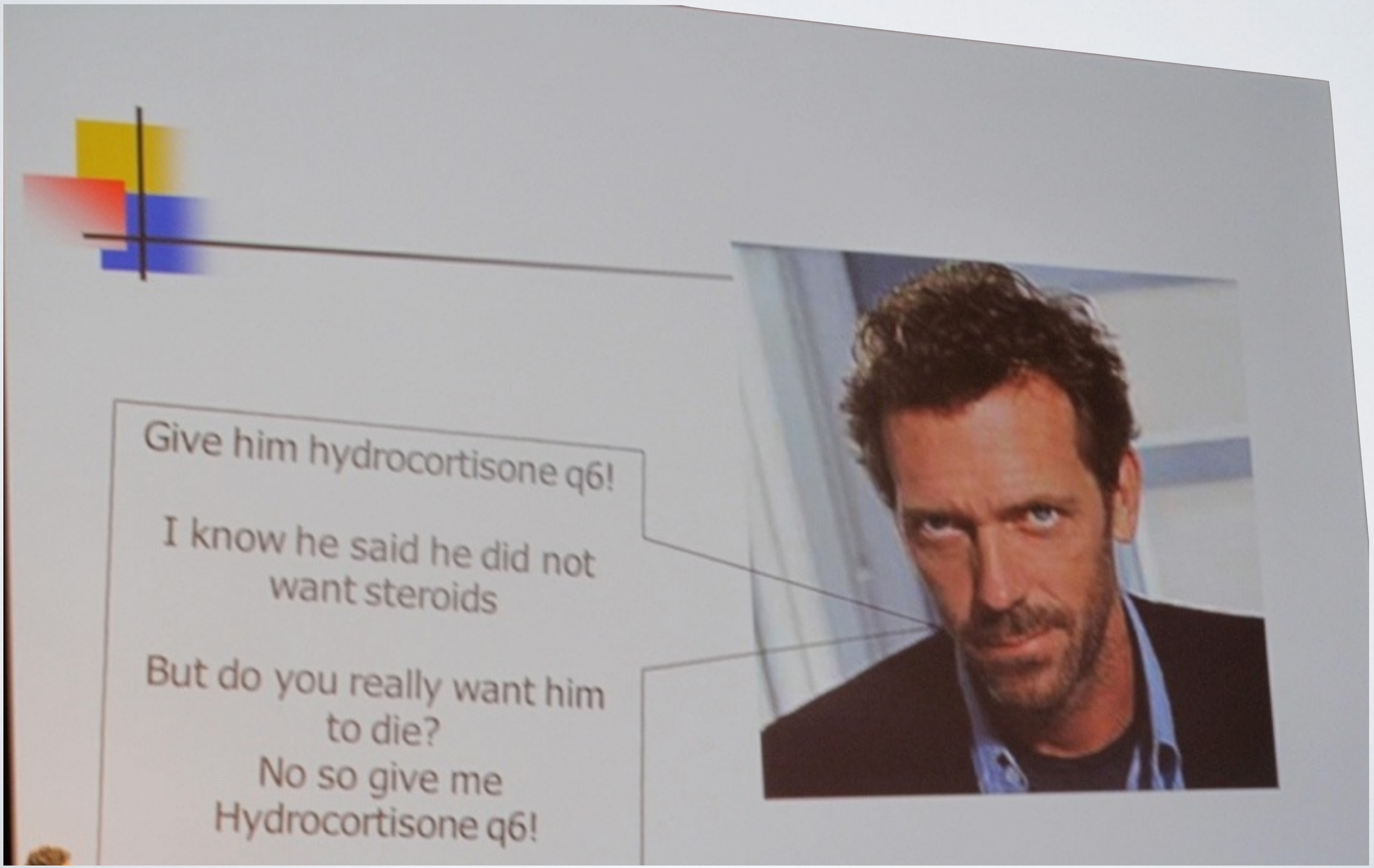
BRUSSELS-
UNFORGETTABLE LECTURES

BRUSSELS -
PEERING INTO THE FUTURE OF MEDICINE

Tobacco Smoke Enema (1750s-1810s)
The tobacco enema was used to infuse tobacco smoke into a patient's rectum for various medical purposes, primarily the resuscitation of drowning victims. A rectal tube inserted into the anus was connected to a fumigator and bellows that forced the smoke towards the rectum. The warmth of the smoke was thought to promote respiration, but doubts about the credibility of tobacco enemas led to the popular phrase "blow smoke up one's ass."

BRUSSELS -
STATE OF THE ART APPROACH TO LIVER FAILURE

BRUSSELS -
A CHANCE TO HEAR WORLD FAMOUS MEDICAL AUTHORITIES

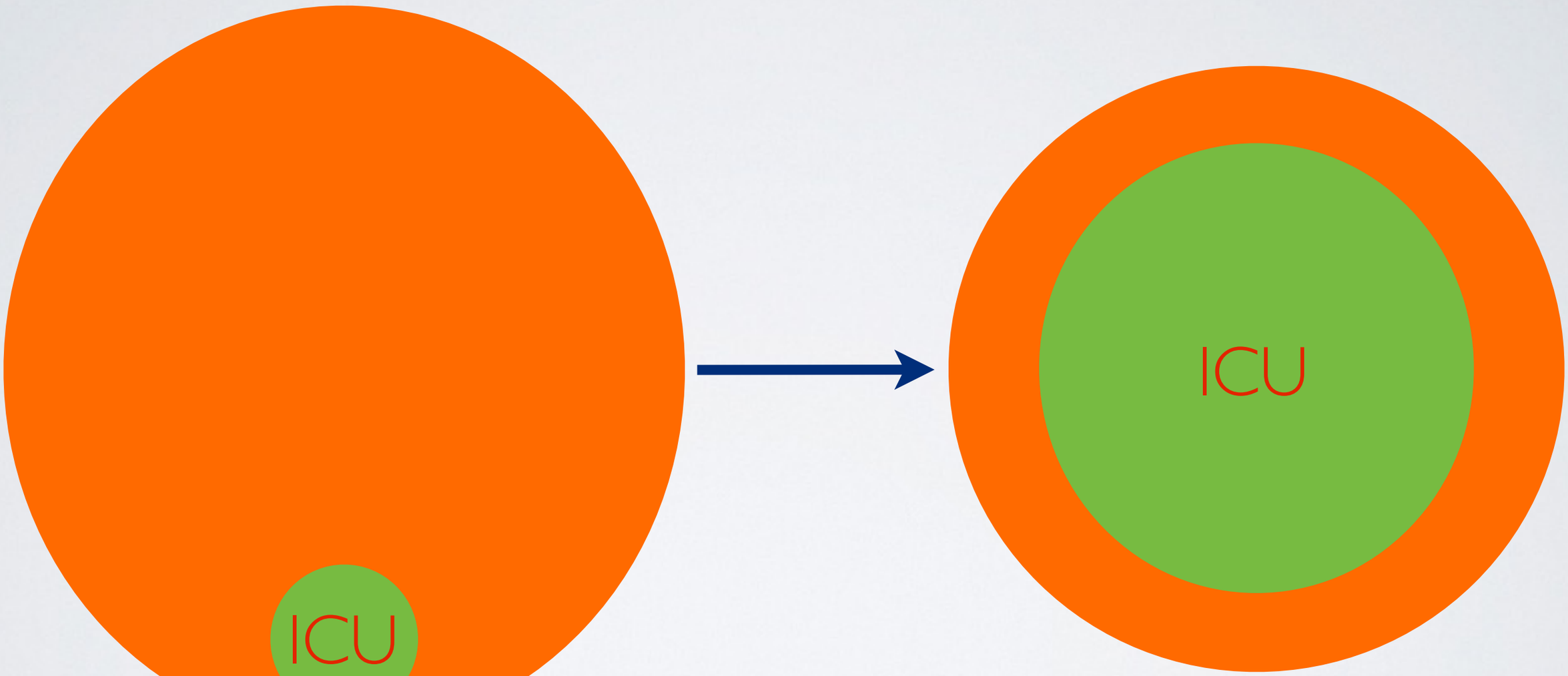


Subjects covered

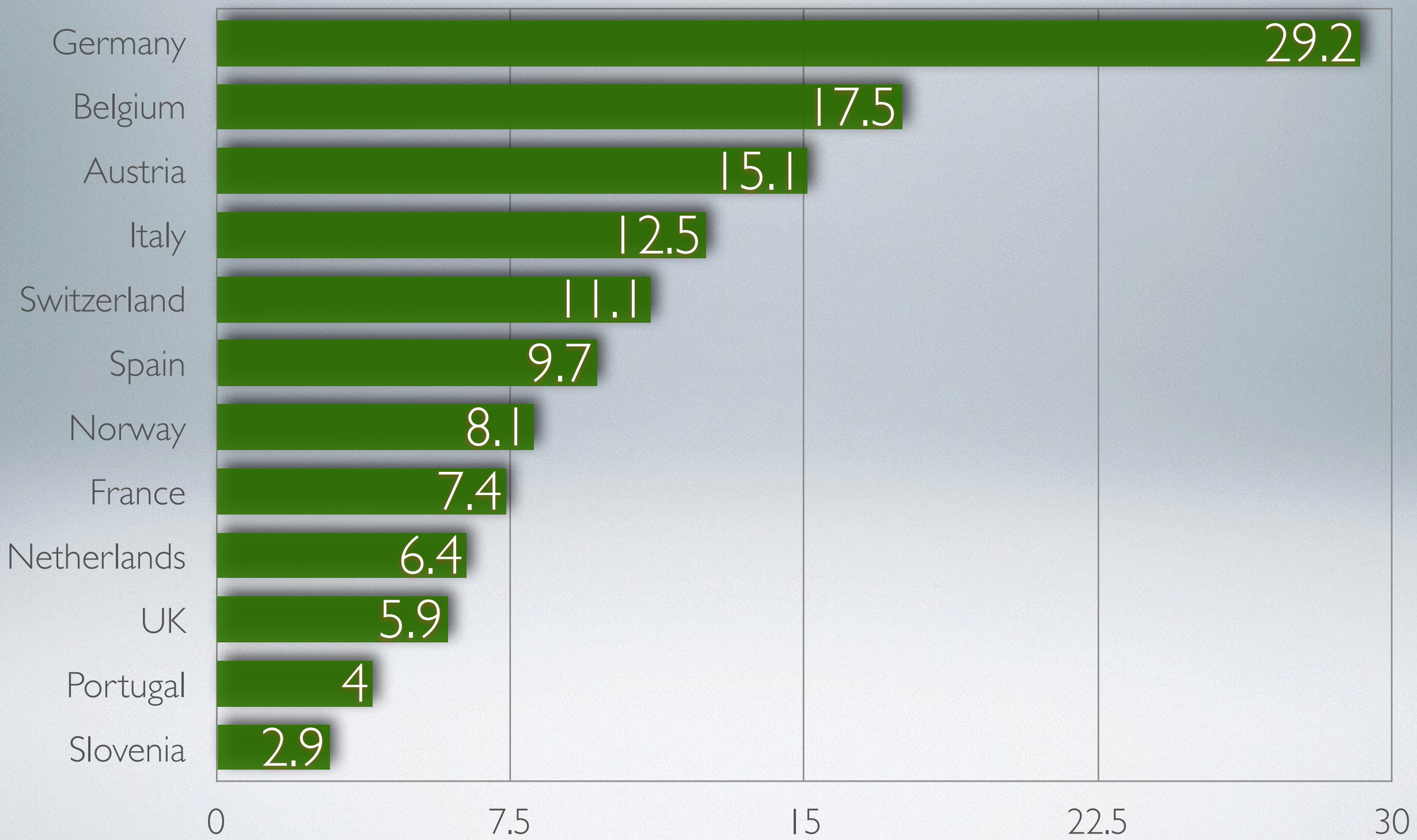
- ICU in the future
- High dose Insulin
- Role of Heart Failure in Failure to Wean
- Fluid Optimisation
- Contrast Induced Acute Kidney Injury in ITU
- Early mobilisation in ARDS
- Chronic Effects of Acute Inflammation
- Iron in the Critically Ill
- Reversal of Vitamin K antagonists in the bleeding patient

ITU in the Future

The Hospital Structure is Changing

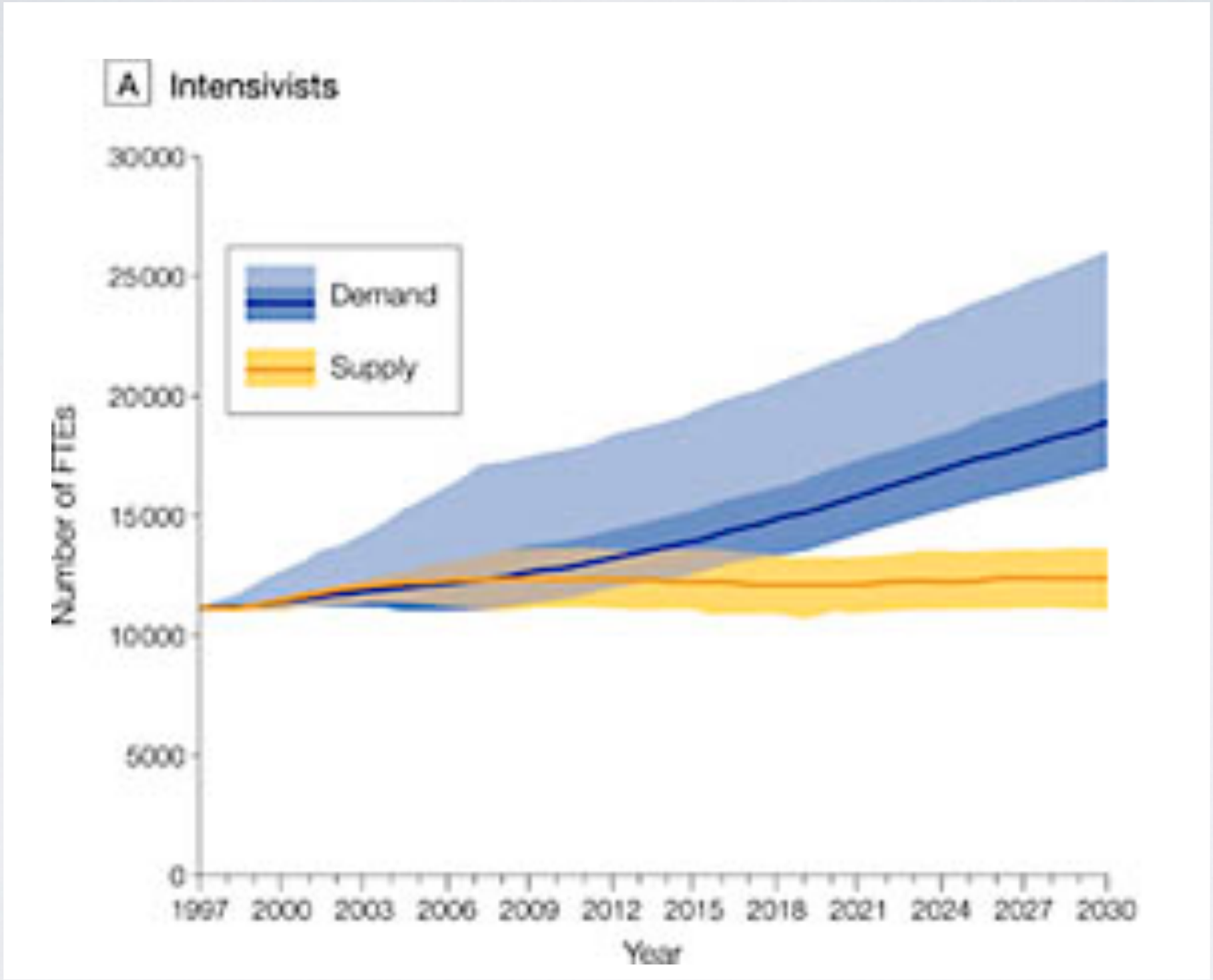


Number of ICU beds / 100,000 of population



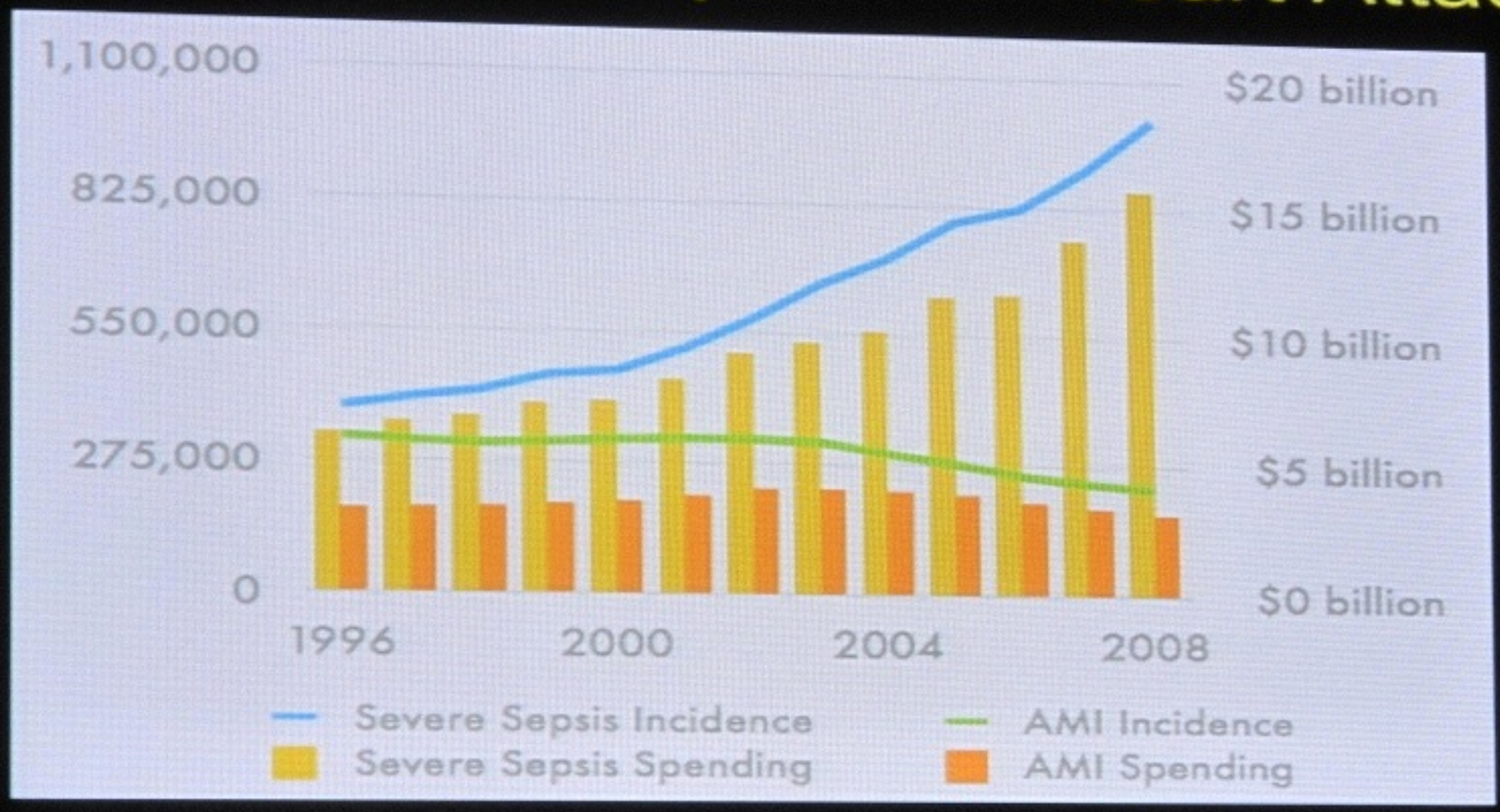
ESICM 2012

Current and Projected Workforce Requirements for Care of the Critically Ill



JAMA. 2000;284(21):2762-2770

Public Health: Sepsis vs. Heart Attacks

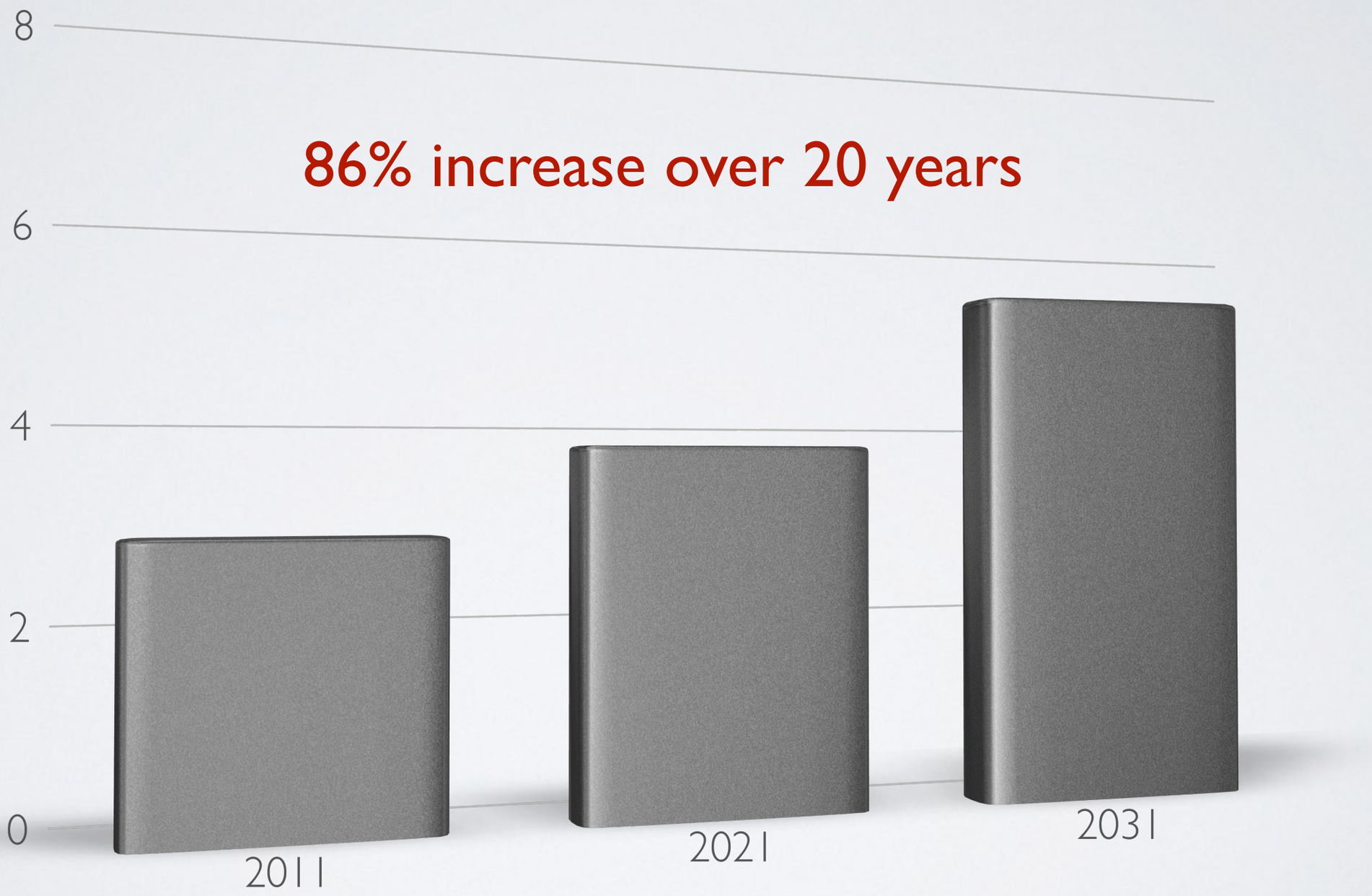


Iwashyna T, JAGS 2012

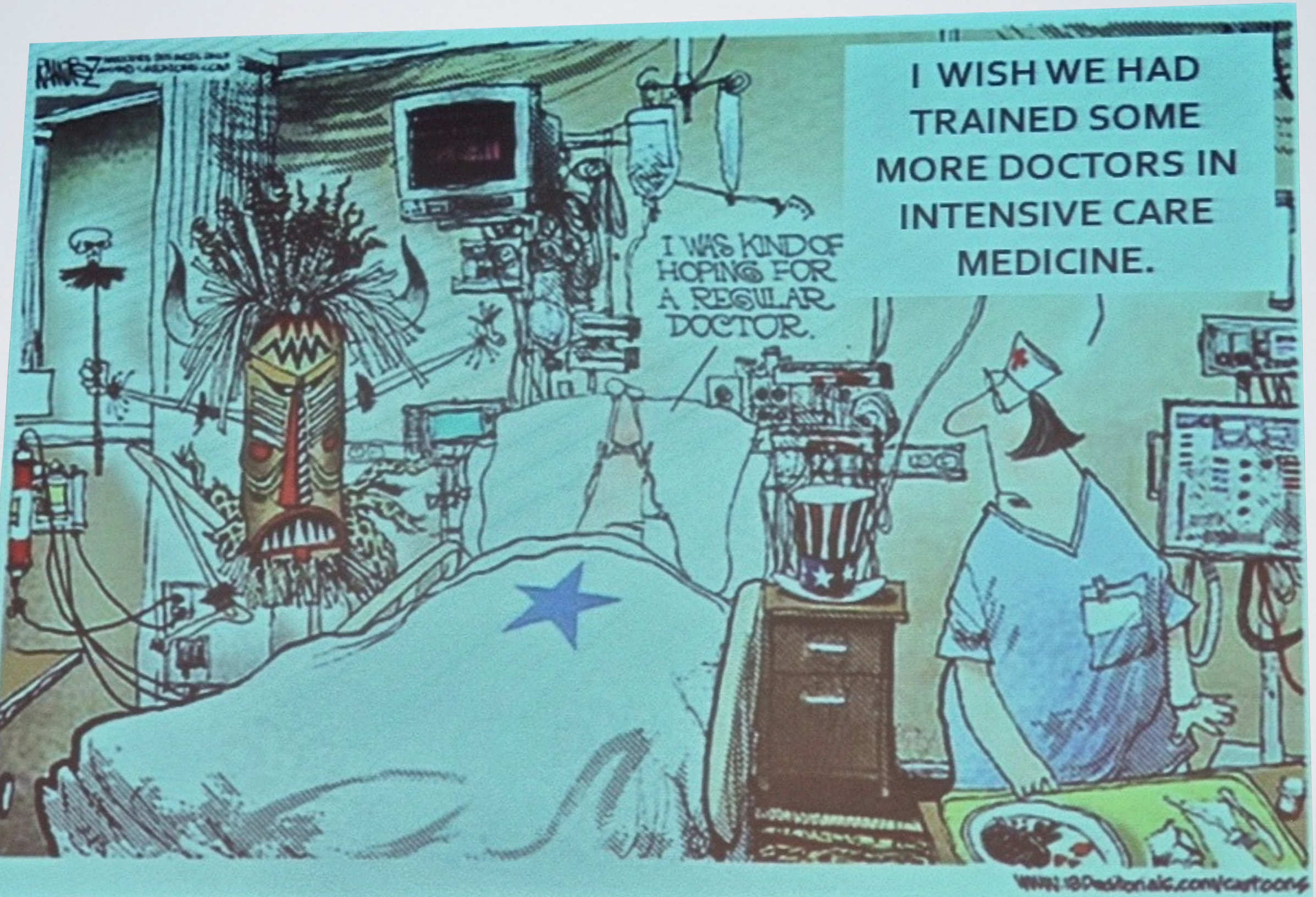
Projected of Over 80s in UK

UK Office of National Statistics

Population size in millions



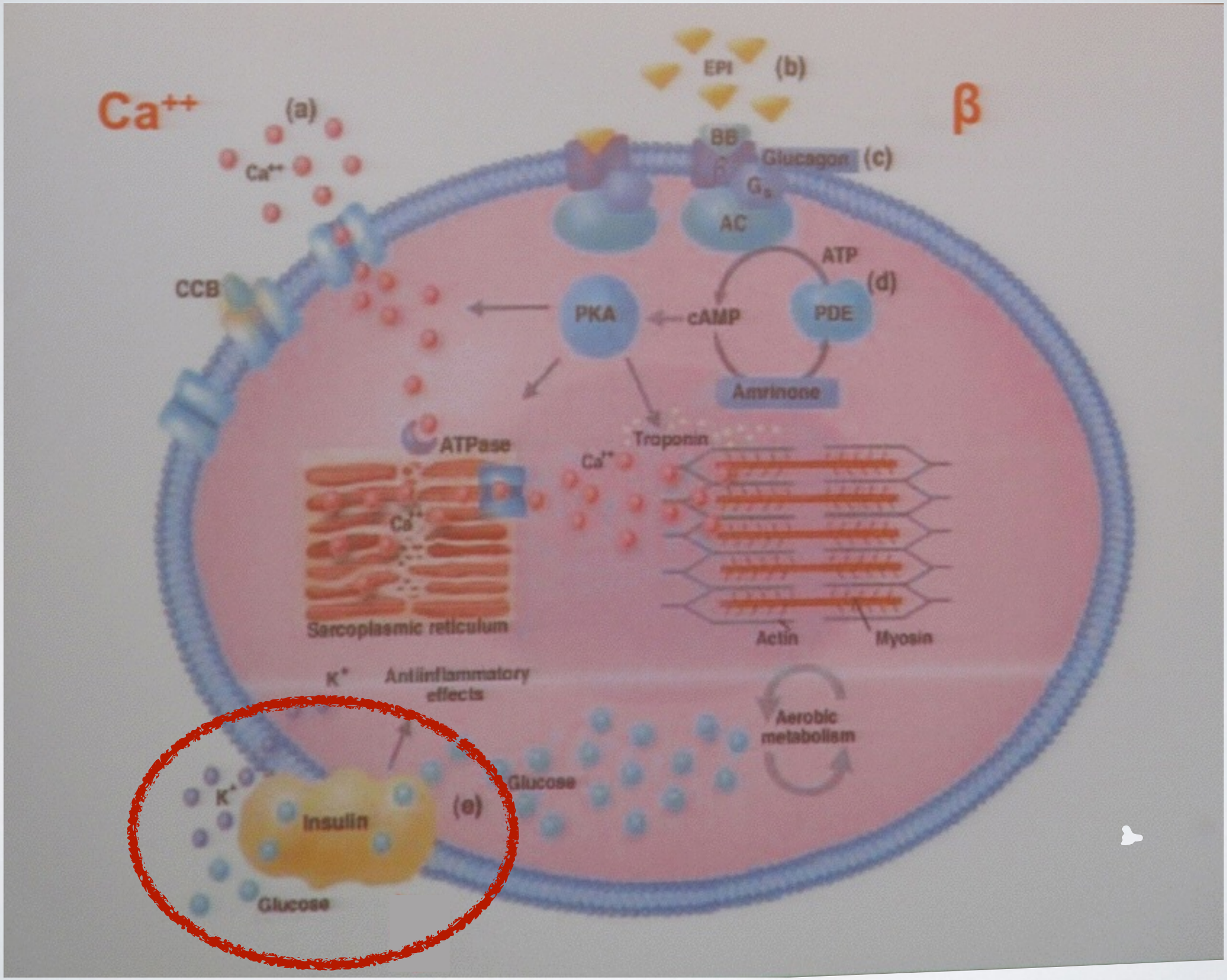
BRUSSELS -
A UNIQUE EDUCATIONAL EXPERIENCE



High dose Insulin

Research Hypothesis

- Insulin's effects on haemodynamics continue into a dosing range **far above** that which achieves glucose homeostasis
- Off-setting insulin's depression of glucose and potassium levels may allow safe exploitation of insulin's inotropy and vasodilatory properties into this high-dose range.

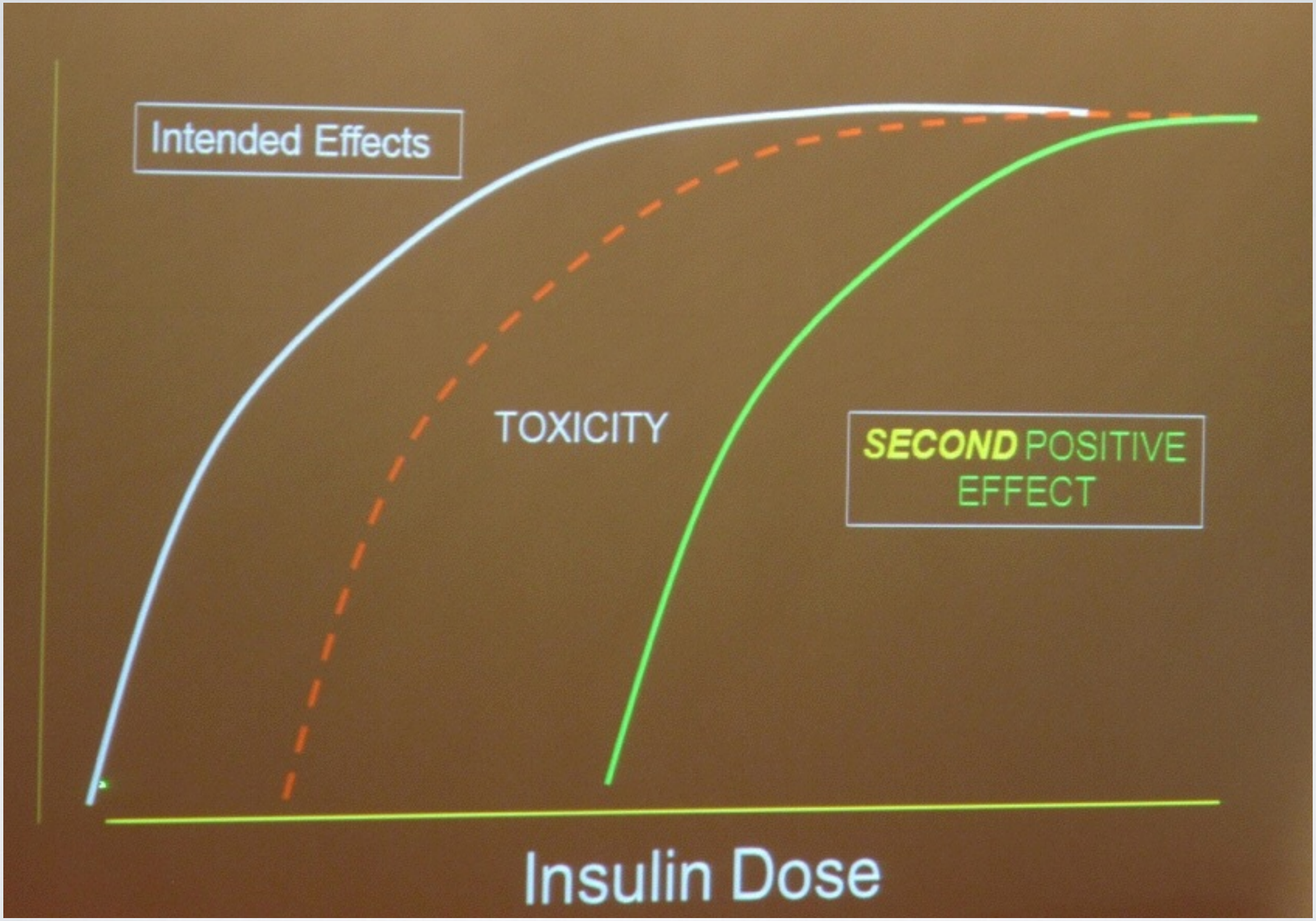

Ca++
(a)
Ca++
EPI
(b)
β
BB
Glucagon
(c)
Gs
AC
ATP
(d)
CCB
PKA
cAMP
PDE
Amrinone
ATPase
Troponin
Ca++
Ca++
Sarcoplasmic reticulum
Actin
Myosin
K+
Antiinflammatory effects
Aerobic metabolism
Glucose
K+
Insulin
(e)
Glucose

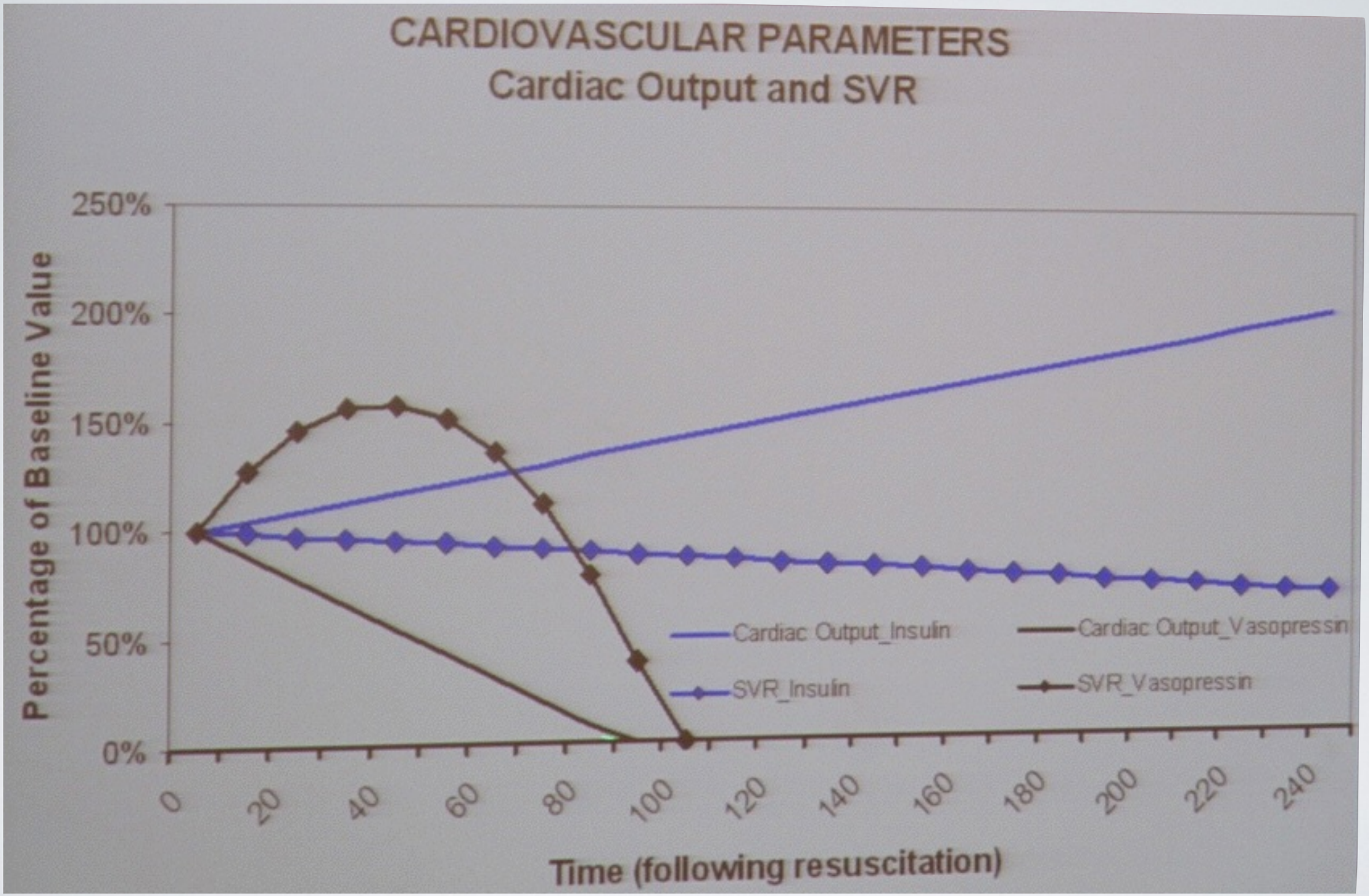
Insulin Cardiovascular Therapy

Uses :

- Congestive Heart Failure
- Post-Pump Cardiac Dysfunction
- Cardio-toxic Overdosage/Poisoning
  - Beta blockers
  - Ca++ Channel Blockers
  - Bupivicaine
    - Other Na+ blockers

Ranges of therapy and toxicity




CARDIOVASCULAR PARAMETERS
Cardiac Output and SVR
Percentage of Baseline Value
250%
200%
150%
100%
50%
0%
0
20
40
60
80
100
120
140
160
180
200
220
240
Time (following resuscitation)
Cardiac Output_Insulin
Cardiac Output_Vasopressin
SVR_Insulin
SVR_Vasopressin

Clinical Translation of HDI

- 65 yr old woman, o/d on:
  - Atenolol, Venlafaxine, Amitriptyline
- Refractory to pressors and **moderate** dose insulin, glucagon, adrenaline, atropine and calcium

- "Terminal shock"
- Started Very high dose insulin
  - 1 U/kg/hr increments q 10 min until **10 U/kg/hr**
  - Near immediate improvement in CV function
  - CO rose from 3.5 to 11 L/min
- High functioning survival

Holger J Clin Tox 2009

Consecutive HDI case series

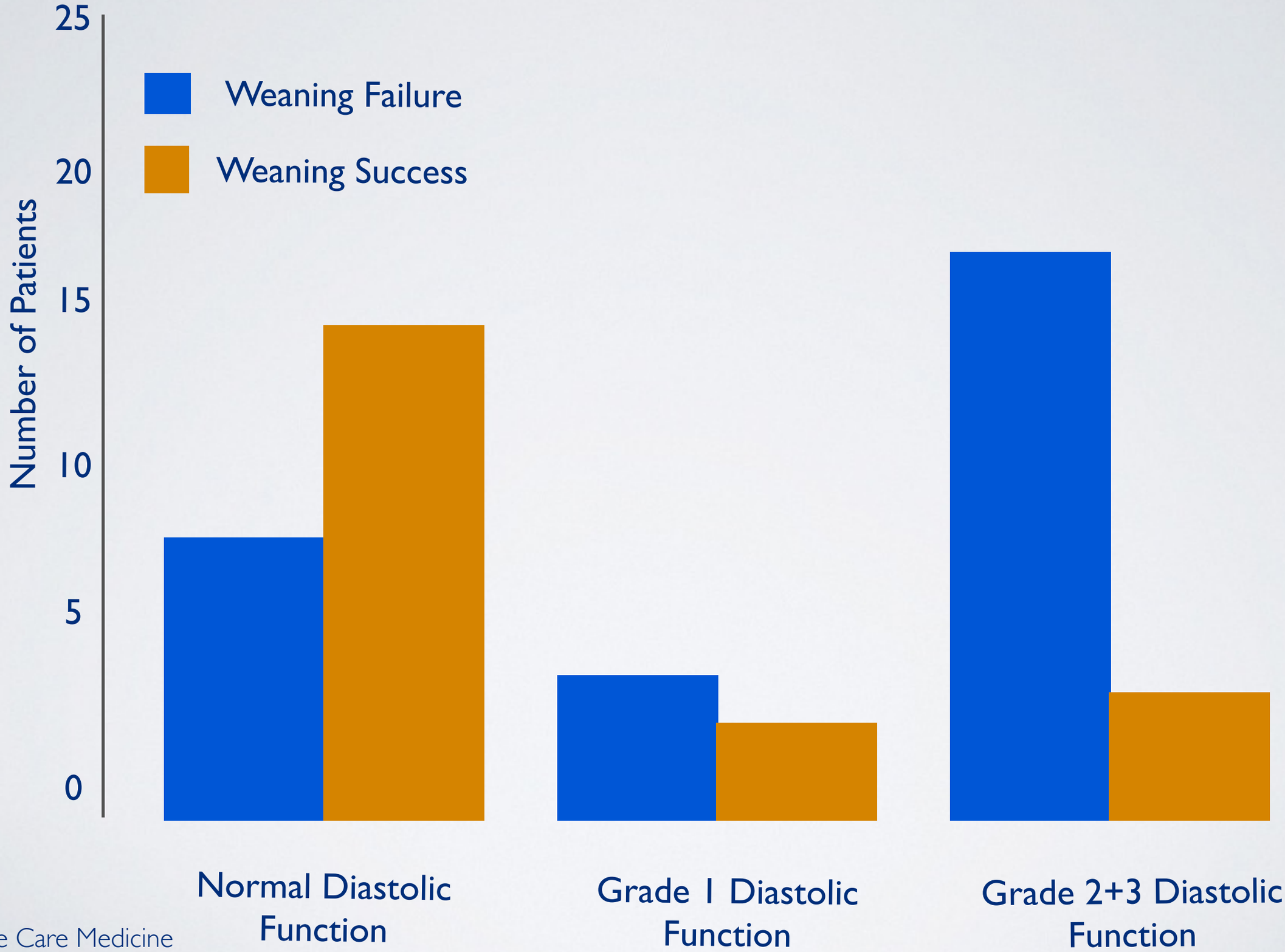
- 12 patients treated with HDI
  - 5 Beta blocker o/d
  - 4 combined Ca++ channel/beta blocker o/d
  - 1 TCA
  - 2 polydrug o/d
  - 6 failed vasopressor/adrenaline therapy

- An initial HDI bolus was used in all 12 patients
- Mean maximum HDI infusion rate : 8.4 U/kg/hr
- Mean duration of HDI 25.5 hrs
- Mean duration of glucose infusion post-HDI : 21 hrs

- **11 of 12 patients survived.**

Role of Heart Failure in Failure to Wean

New insights into weaning failure: Left ventricular diastolic dysfunction is a key player

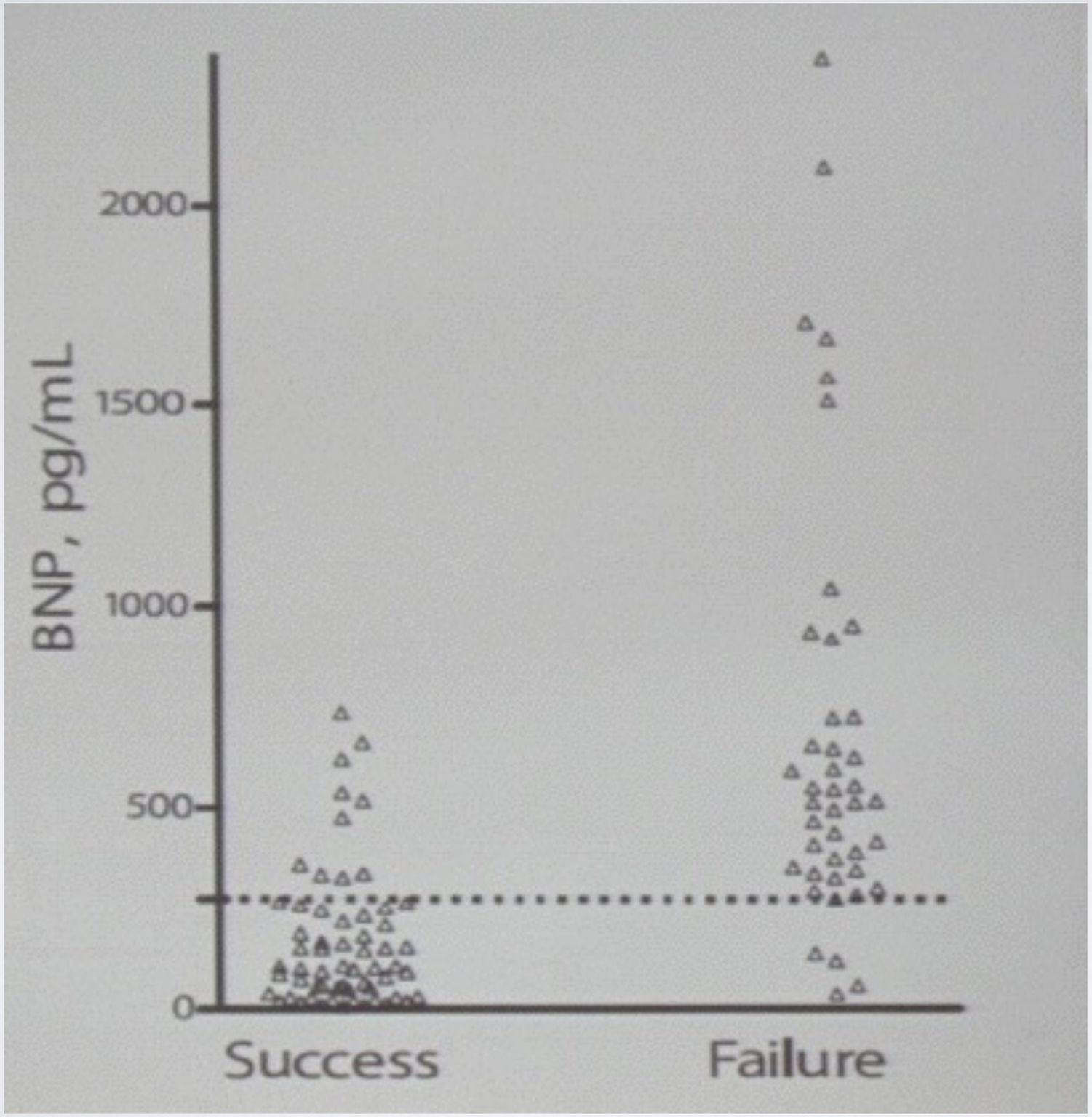


Intensive Care Medicine
2011;37:1976-1985

Weaning in heart failure

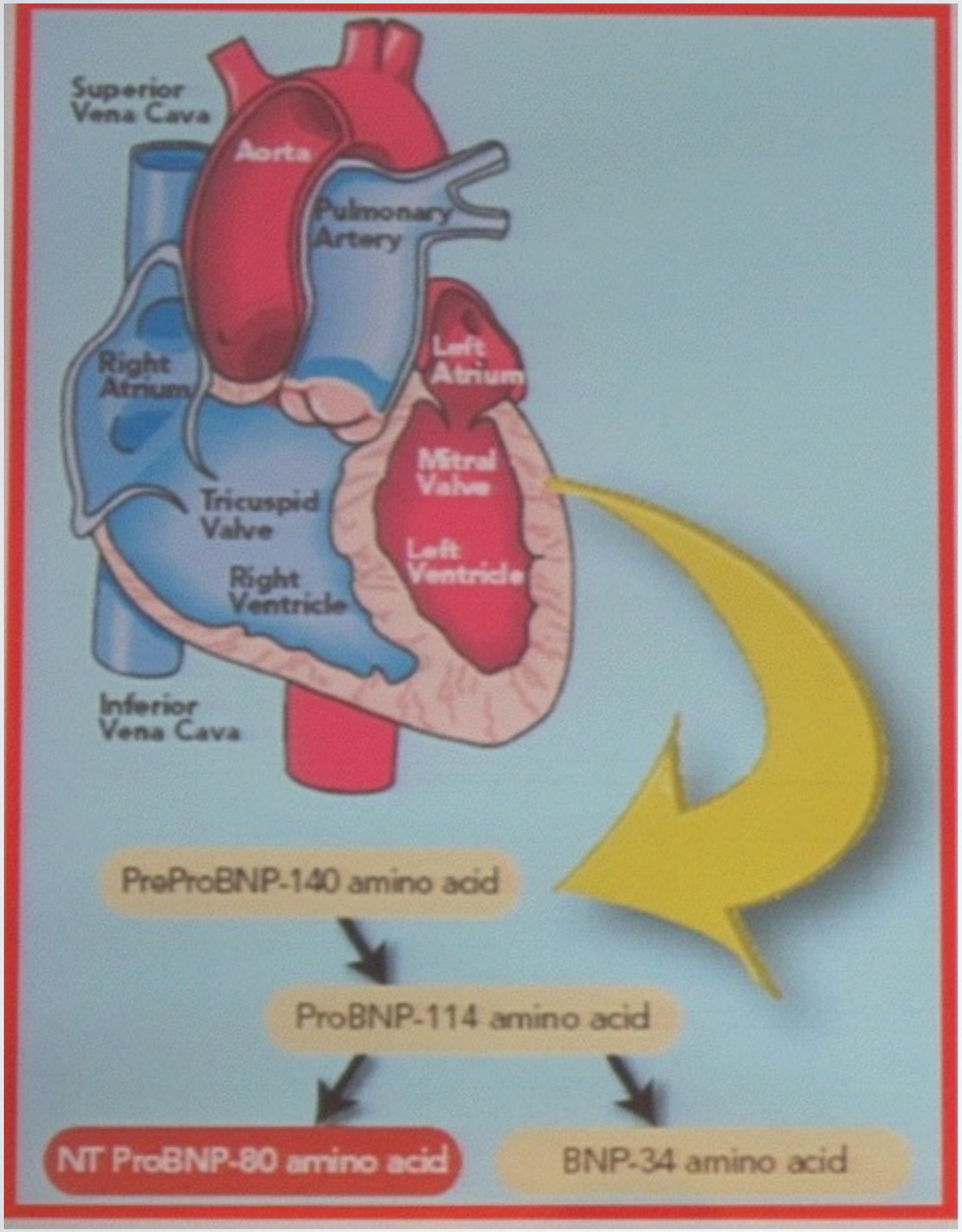
- Weaning is an exercise: increased heart stress
- Weaning failure related to cardiac failure is frequent (**~ 50%**)
- Echocardiography may help intensivists to detect high risk patients
- How it can change the evolution remains to be elucidated

B-type natriuretic peptide and weaning from mechanical ventilation



Intensive care medicine 2006;32:1529-1536

B-type natriuretic peptide

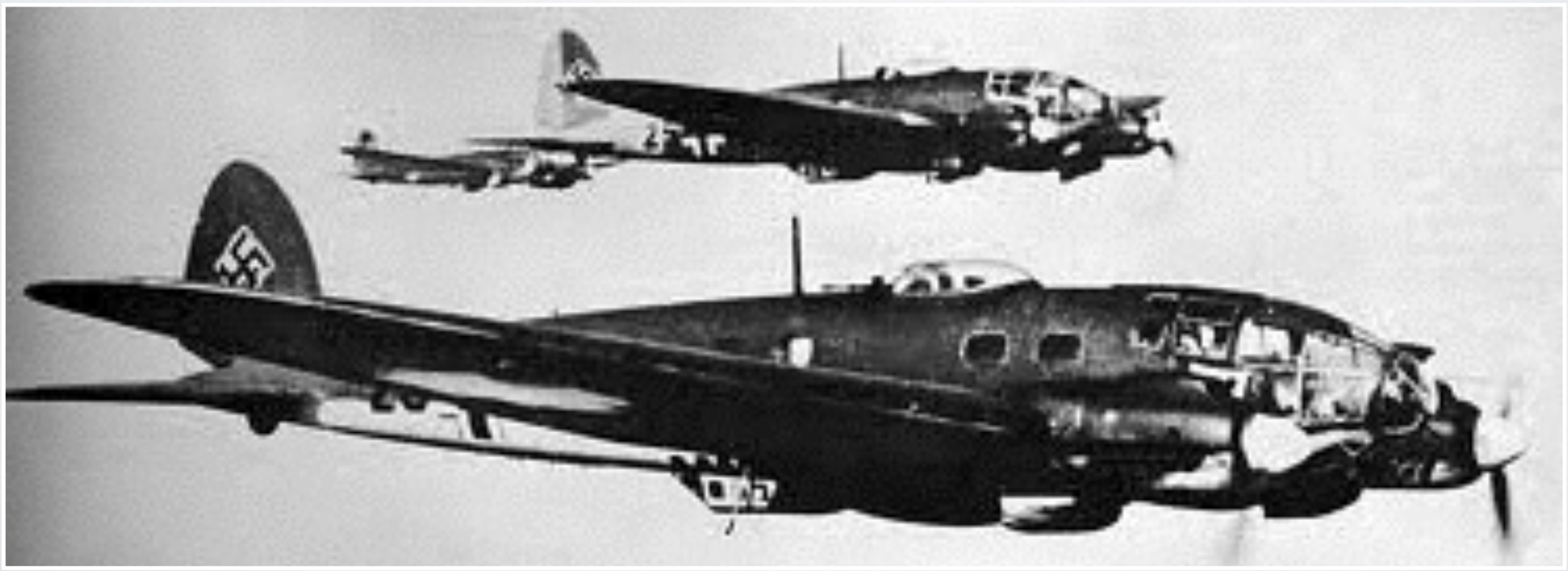


BNP plasma 1/2 life = 20 min

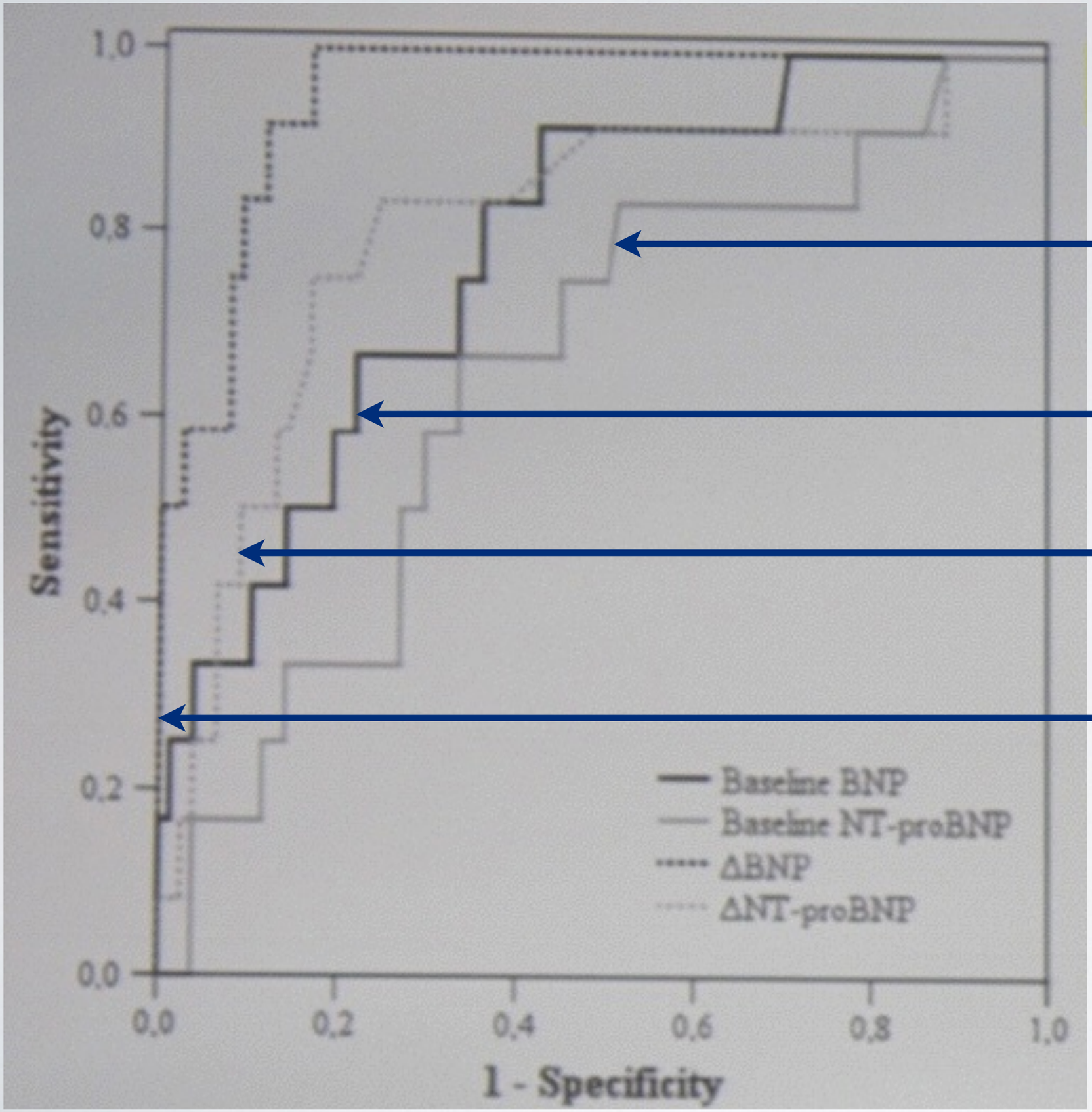
NT-pro BNP plasma 1/2 life = 2 hrs

Receiver Operating Curve

or



BNP to predict weaning failure



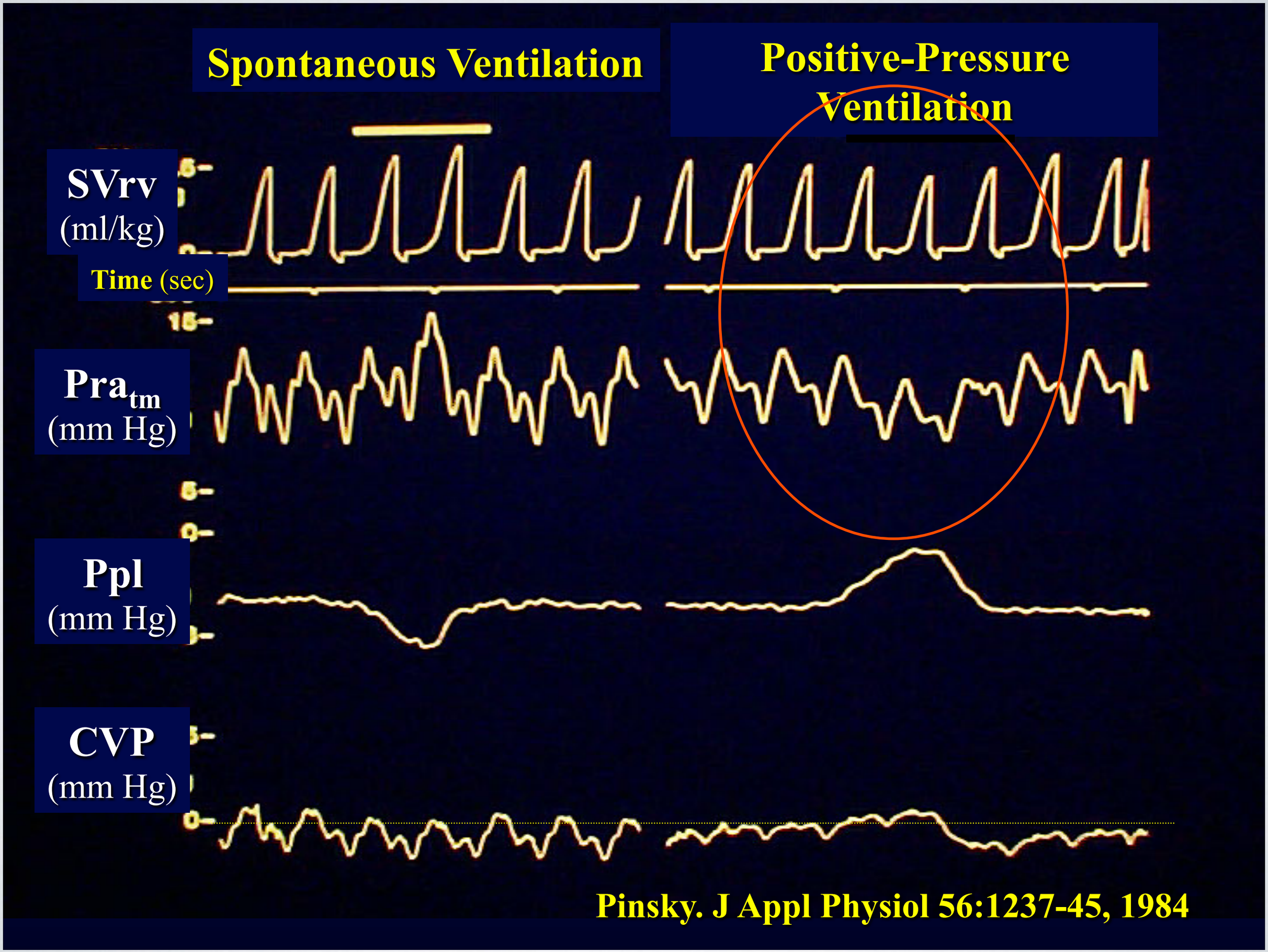
Baseline NT-proBNP >263 ng/L AUC-80

Baseline BNP >1343 ng/L AUC-66

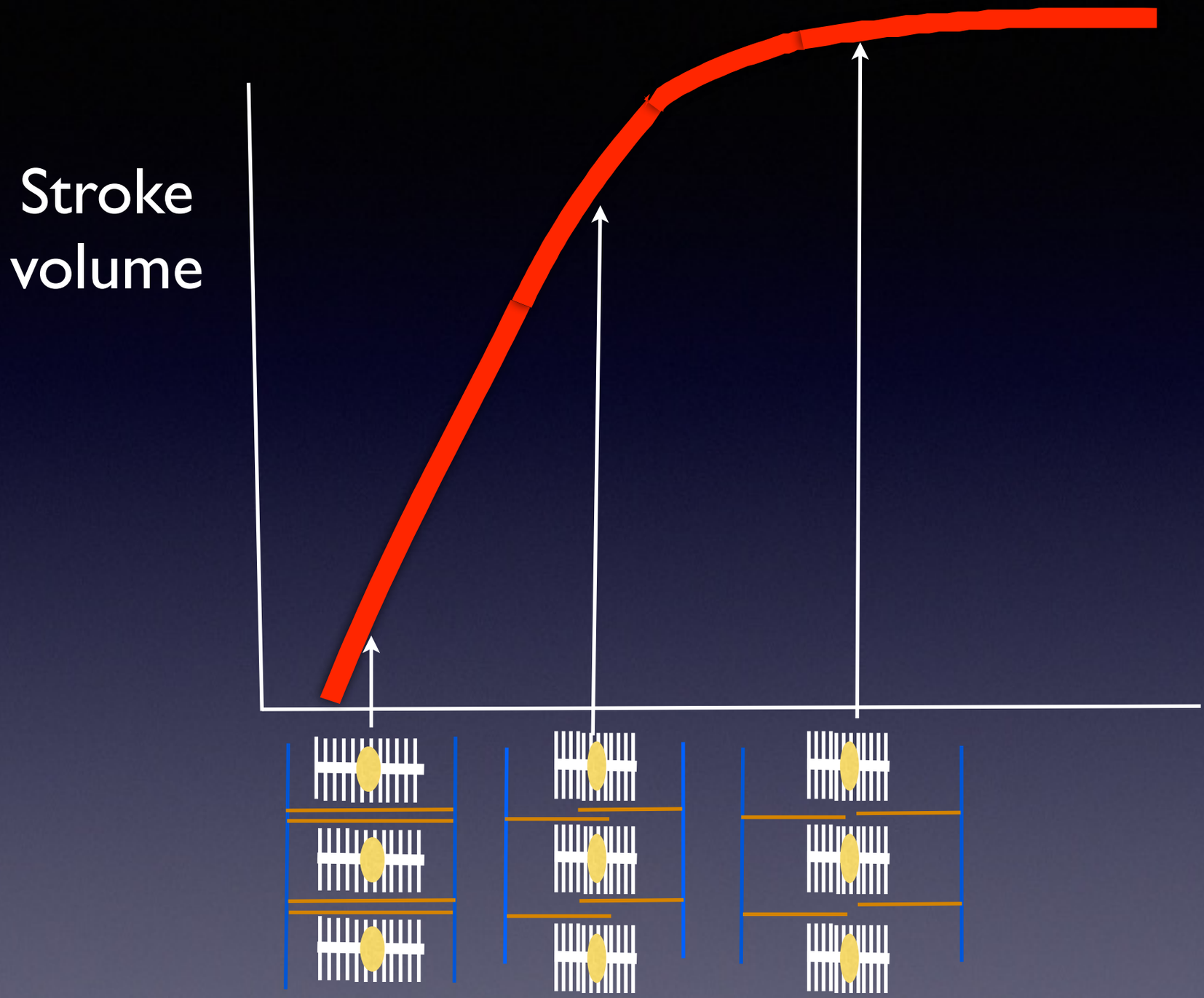
ΔNT-proBNP >21 ng/L **AUC-81**

ΔBNP >48 ng/L **AUC-95**

Fluid Optimisation



Pinsky. J Appl Physiol 56:1237-45, 1984



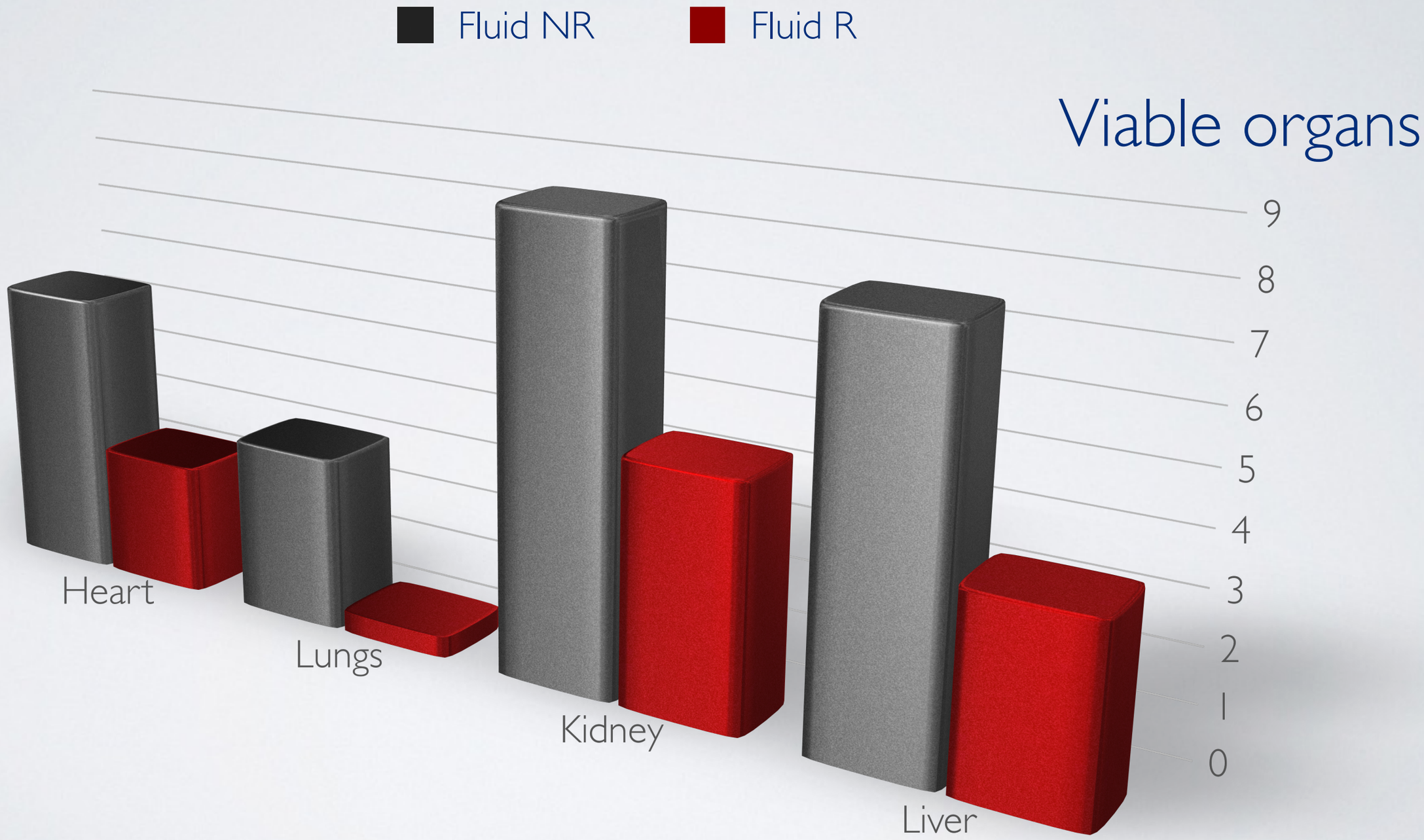
Preload (= muscle stretch)

What does this bag of lettuce have to do with Starling's Law?

807 m

Illustration of transmural pressure

Fluid responsiveness is associated with lower organ yield from brain-dead donors

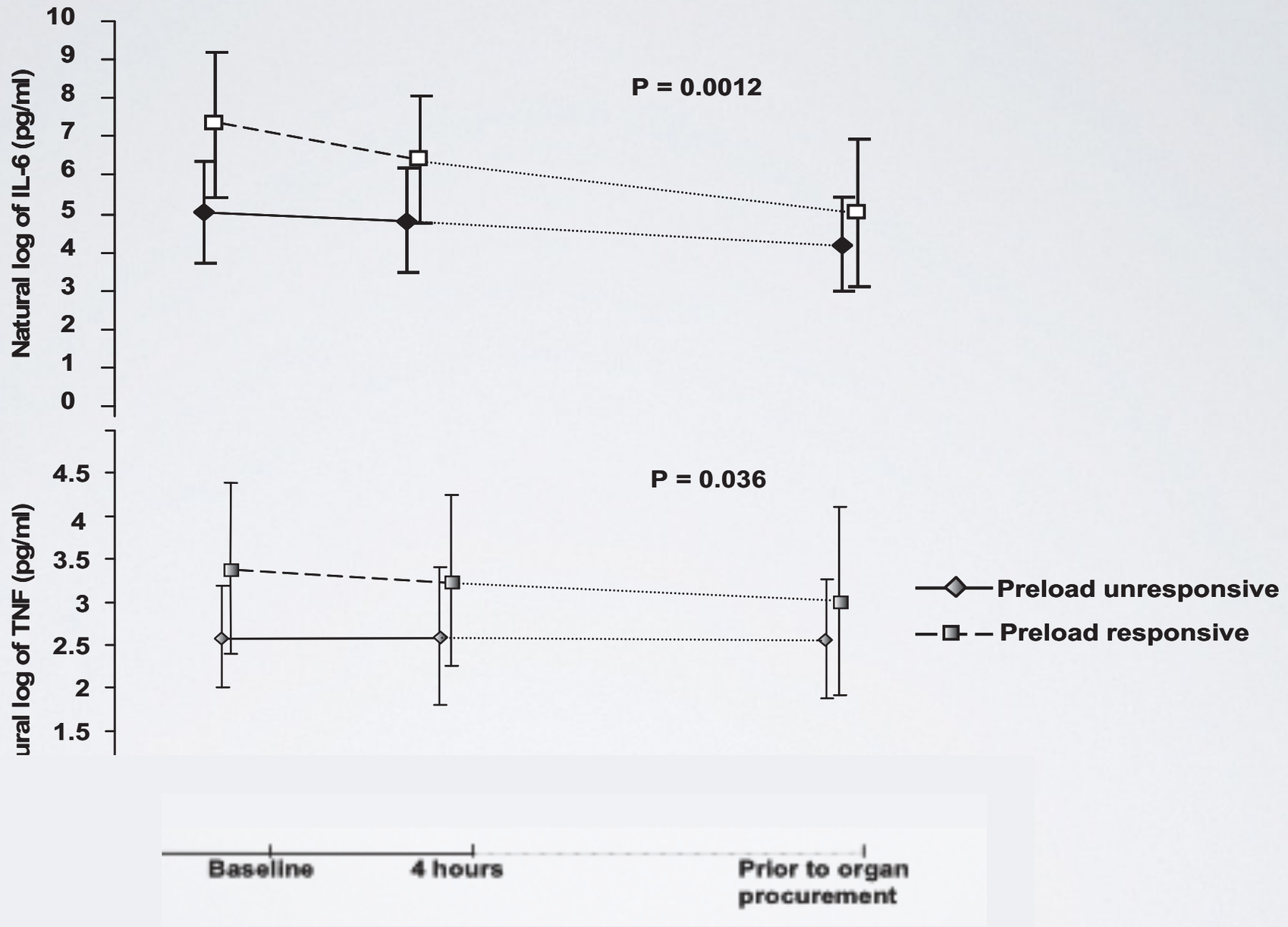


Murugan et al. Crit Care Med 2009

Preload responsiveness and inflammation

IL-6

TNF



Crit Care Med 2009 Vol. 37, No. 8

Importance of Venous Congestion for Worsening of Renal Function

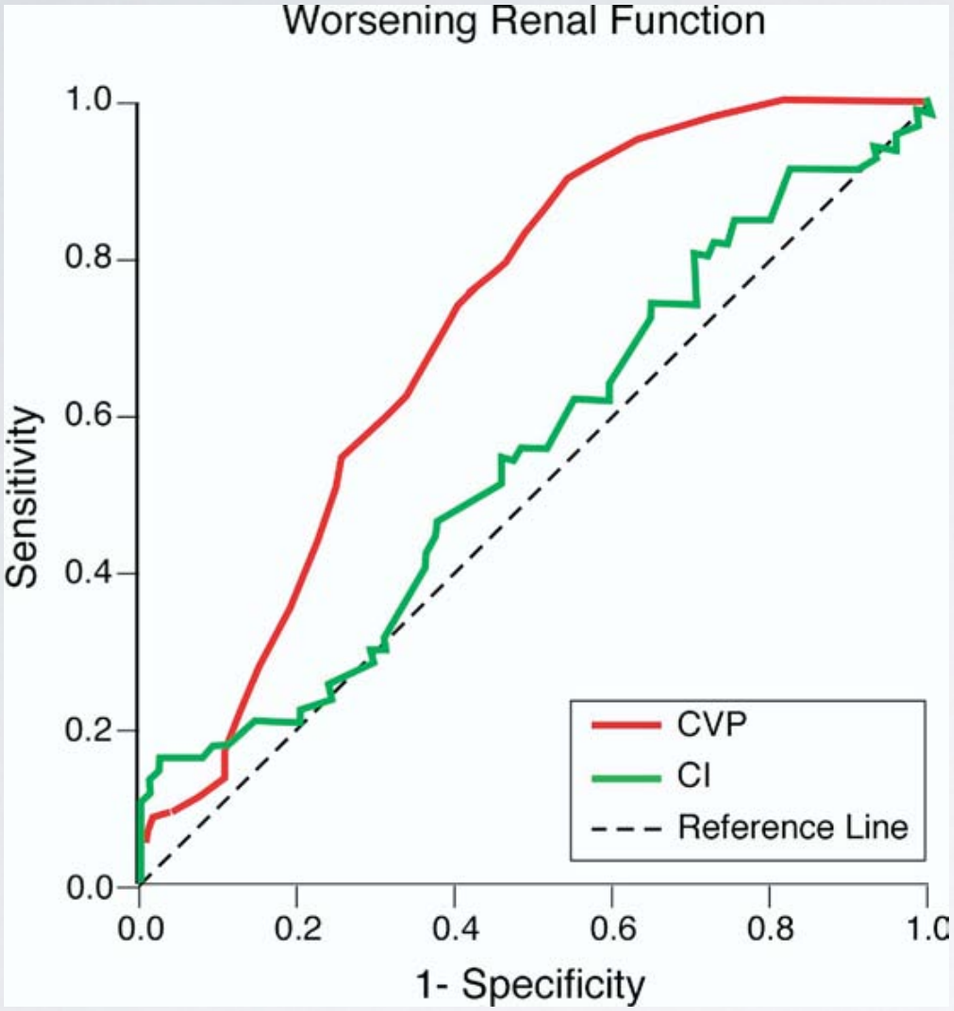


Figure 2 **ROC Curves for CVP and CI on Admission for the Development of WRF**

ROC = receiver-operating characteristic; WRF = worsening renal function; other abbreviations as in Figure 1.

JACC Vol. 53, No. 7, 2009 February 17, 2009:589–96

Contrast Induced Acute Kidney Injury in ITU

Contrast induce AKI

- 11% of hospital acquired AKI
- Incidence 2% - 7% if CKD
- 0.5-2% require RRT

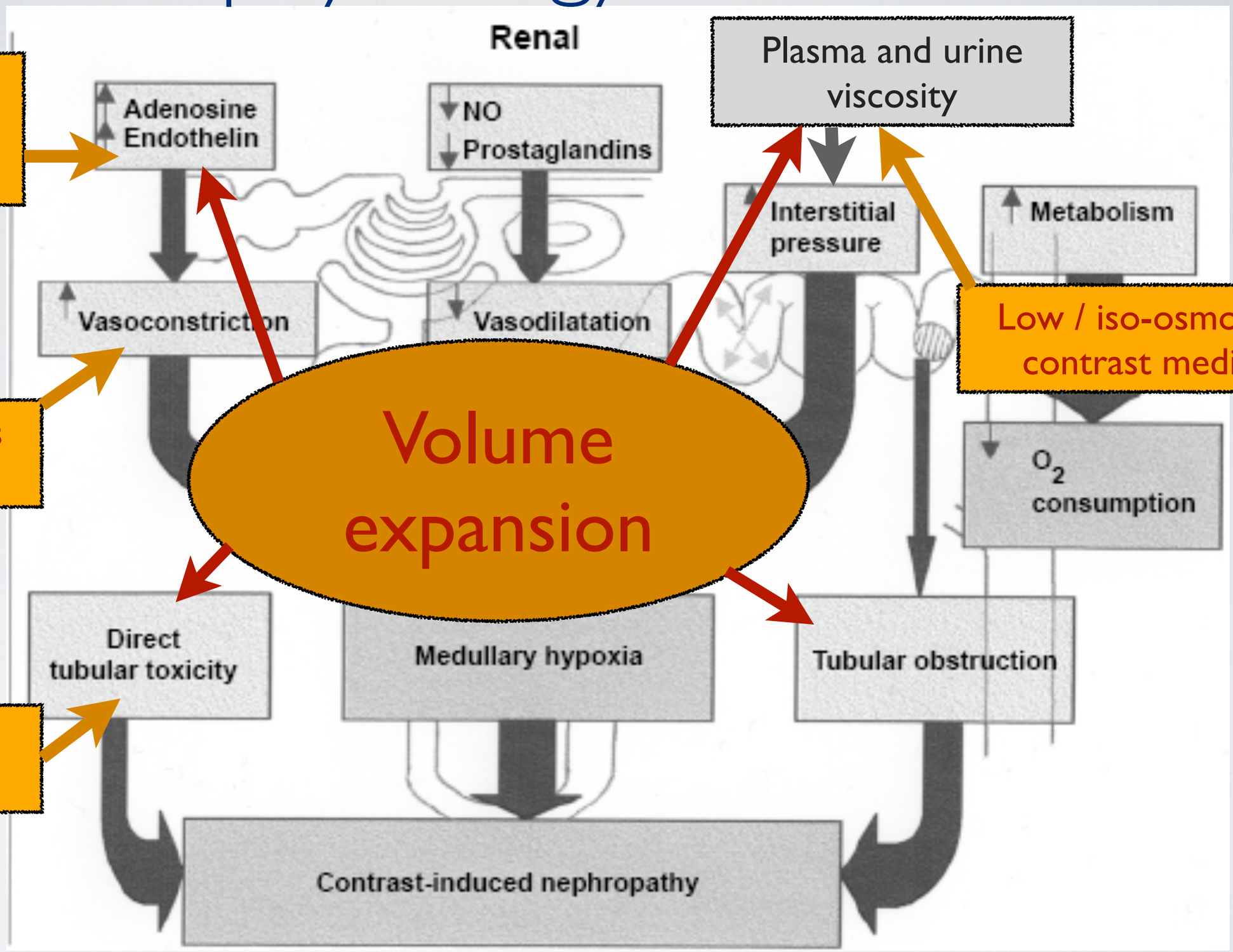
- Risk factors:
  - CKD
  - Diuretics
  - Vasopressors
  - Hypotension

Pathophysiology of CIN

Adenosine antagonists (aminophylline)

Renal vasodilators (fenoldepam)

Anti-oxidants Vitamin C, NAC,



Am J Roentgenol. 2004;183

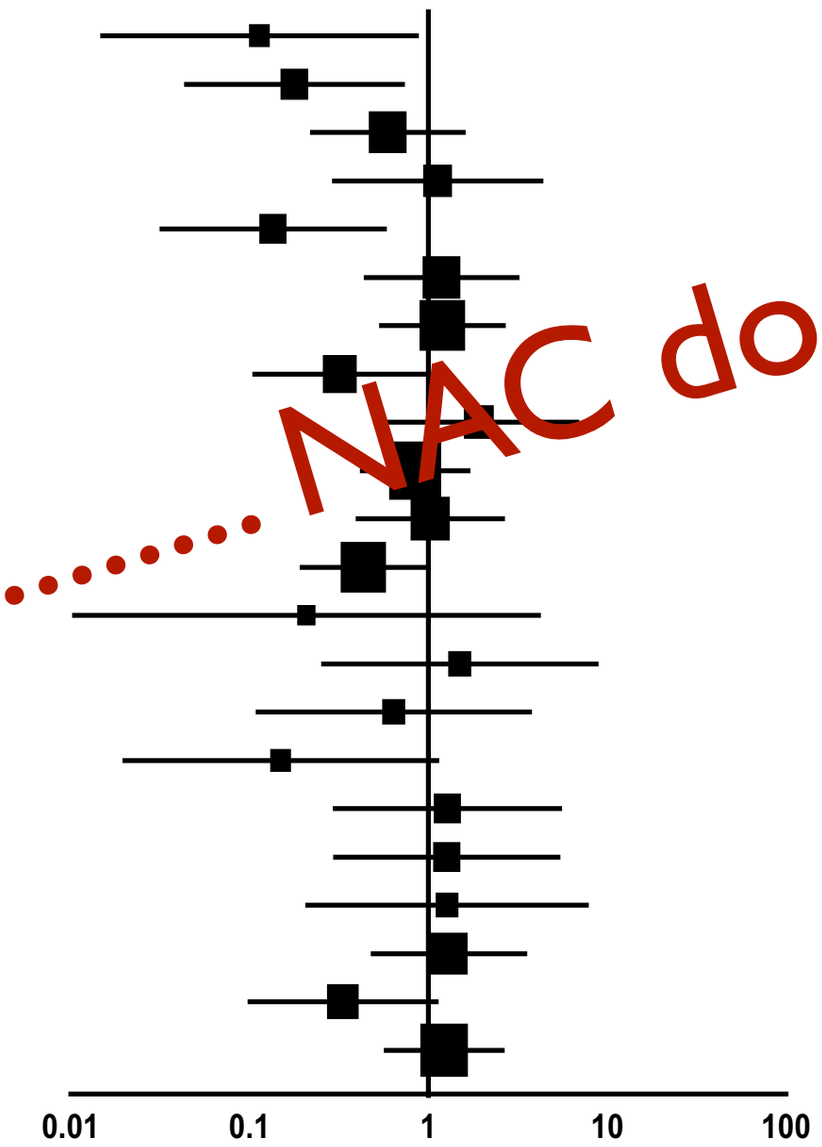
Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and vascular angiography: (ACT trial)

- Standard dose (600-1200 mg bid p.o.):
  - cheap
  - maybe harmless
  - **ineffective**
- Adverse effects:
  - salivation
  - allergic reaction

Circulation 2011; 124:1250

A meta-analysis of N-acetylcysteine in contrast-induced nephrotoxicity

Author, Year (Reference)	CIN* / Total		Relative risk and 95% CI		
	NAC	Control		Relative risk (95% CI)	p-Value
Tepel et al., 2000 [10]	1 / 41	9 / 42		0.11 (0.02-0.86)	0.04
Diaz-Sandoval et al., 2002 [11]	2 / 25	13 / 29		0.18 (0.04-0.72)	0.02
Briguori et al., 2002 [12]	6 / 92	10 / 91		0.59 (0.23-1.57)	0.29
Vallero et al., 2002 [13]	4 / 47	4 / 53		1.13 (0.30-4.26)	0.86
Shyu et al., 2002 [14]	2 / 60	15 / 61		0.14 (0.03-0.57)	0.01
Allaqaband et al., 2002 [15]	8 / 45	6 / 40		1.19 (0.45-3.12)	0.73
Durham et al., 2002 [16]	10 / 38	9 / 41		1.20 (0.55-2.63)	0.65
Kay et al., 2003 [17]	4 / 102	12 / 98		0.32 (0.11-0.96)	0.04
Loutrianakis et al., 2003 [18]	6 / 24	3 / 23		1.92 (0.54-6.77)	0.31
Azmus et al., 2003 [19]	14 / 196	17 / 201		0.84 (0.43-1.67)	0.63
Gomes et al., 2003 [20]	8 / 77	8 / 79		1.03 (0.41-2.60)	0.96
Nguyen-Ho et al., 2003 [21]	8 / 83	16 / 79		0.43 (0.20-0.95)	0.04
Efrati et al., 2003 [22]	0 / 24	2 / 25		0.21 (0.01-4.12)	0.30
El Mahmoud et al., 2003 [23]	3 / 60	2 / 60		1.50 (0.26-8.66)	0.65
Kefer et al., 2003 [24]	2 / 53	3 / 51		0.64 (0.11-3.68)	0.62
MacNeill et al., 2003 [25]	1 / 21	7 / 22		0.15 (0.02-1.11)	0.06
Oldemeyer et al., 2003 [26]	4 / 49	3 / 47		1.28 (0.30-5.41)	0.74
Goldenberg et al., 2004 [27]	4 / 41	3 / 39		1.27 (0.30-5.31)	0.74
Agrawal et al., 2004 [28]	2 / 11	2 / 14		1.27 (0.21-7.65)	0.79
Fung et al., 2004 [29]	8 / 46	6 / 45		1.30 (0.49-3.46)	0.59
Ochoa et al., 2004 [30]	3 / 36	11 / 44		0.33 (0.10-1.10)	0.07
Webb et al., 2004 [31]	14 / 194	12 / 204		1.23 (0.58-2.59)	0.59



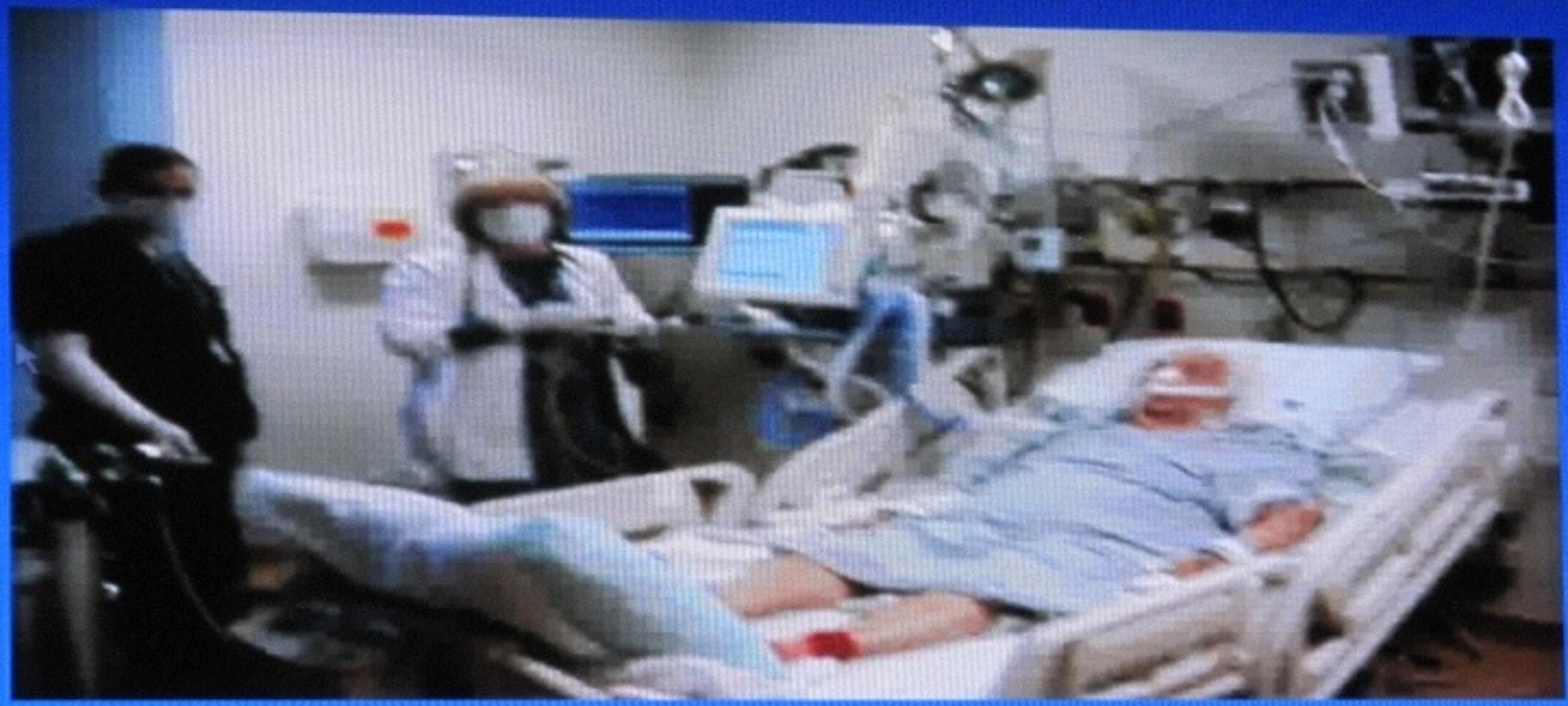
Sorry folks……NAC doesn't work!

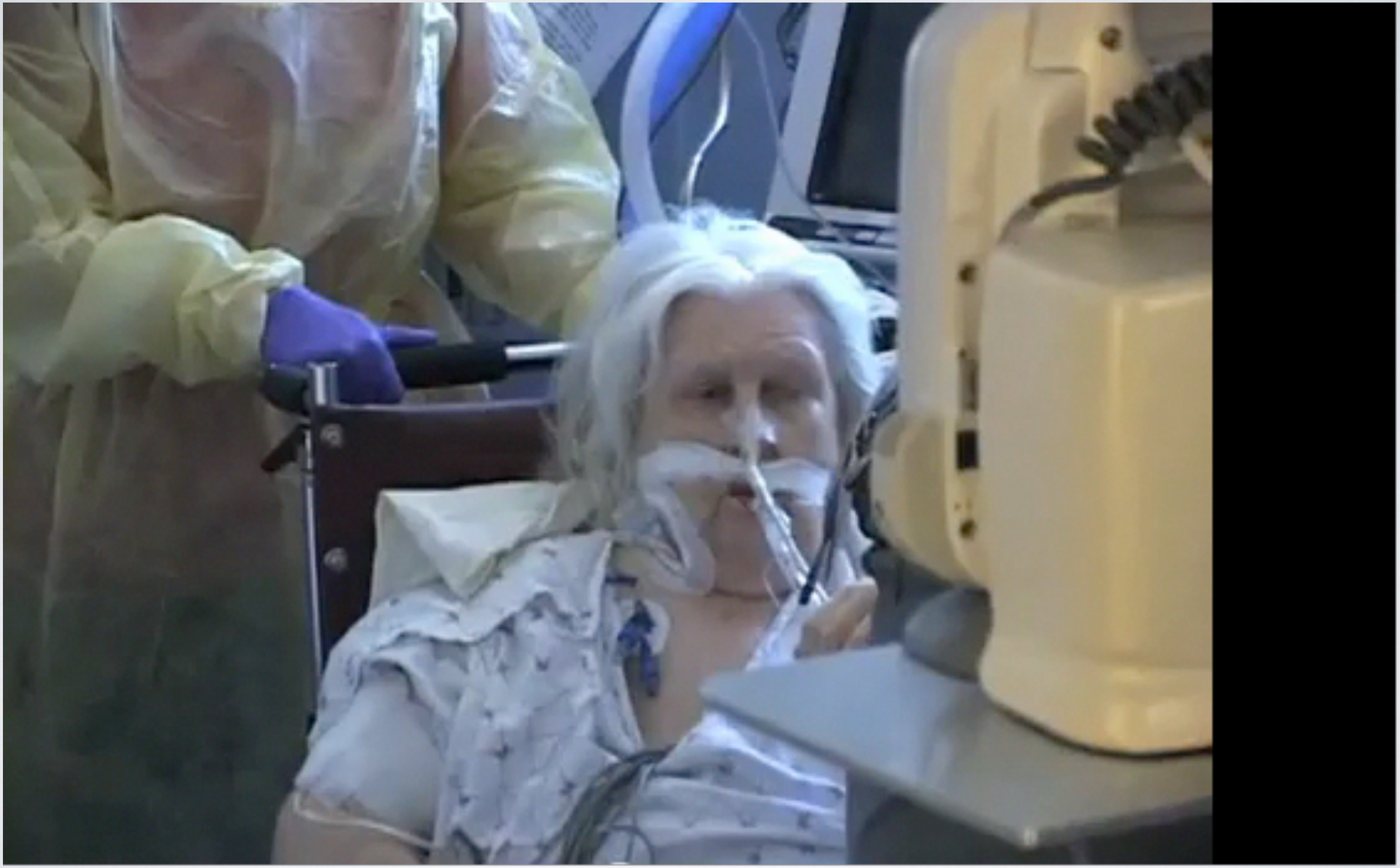
BMC Medicine 2007, 5:32 doi:10.1186/1741-7015

Prevention of CI-AKI Summary

- Control risk factors (avoid nephrotoxins-metformin, aminoglycosides, etc)
- Correct and avoid hypovolaemia (esp. care with diuretics)
- Apply preemptive IV **volume expansion**, if tolerated
- **Preemptive RRT does NOT work**

ABCDE Video - 84 y/o with H1N1 and ARDS





Winner of the "Not My Job" Award

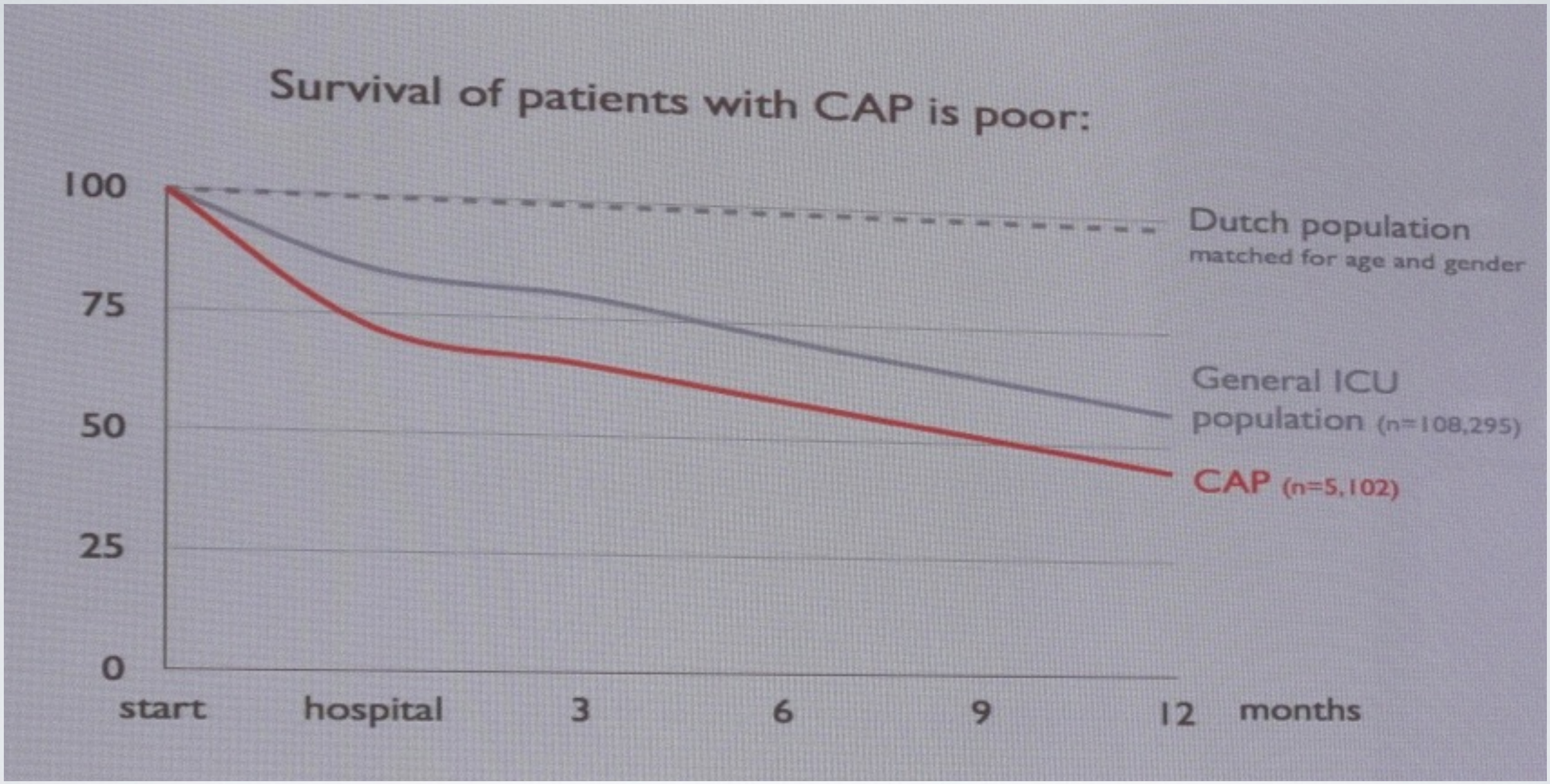
Chronic Effects of Acute Inflammation

Chronic Effects of Acute Inflammation

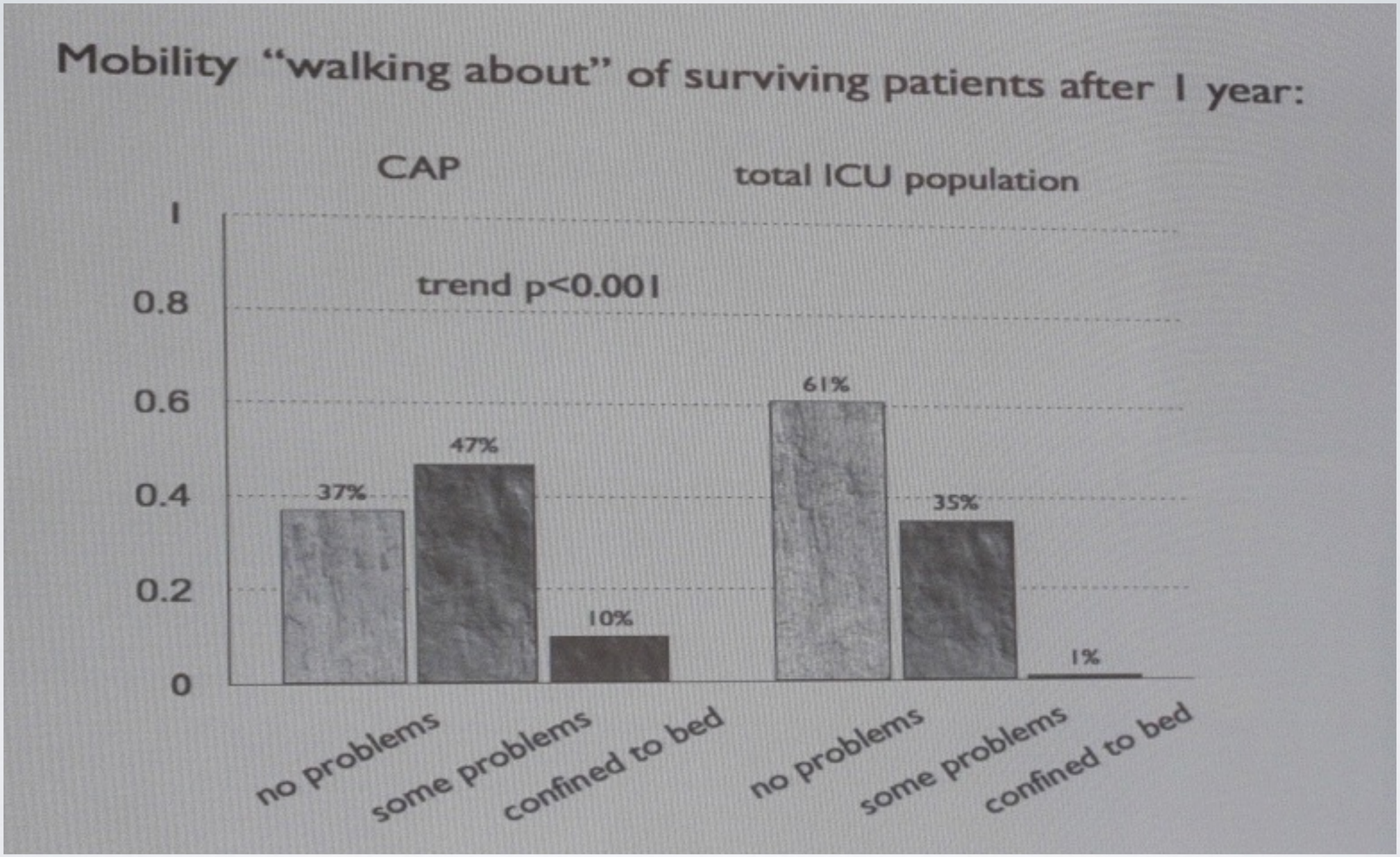
- Chronic disease after life-threatening sepsis
- Long-term Consequences of Severe Sepsis
  - 80% of "recovered" severe septic patients dead in 8 years
  - 40% of severe septic patients "leaving hospital" dead in 4 years

JAMA 1997;277:1058
JAMA 1995;274:338

Long term outcome of CAP



Long term outcome of CAP



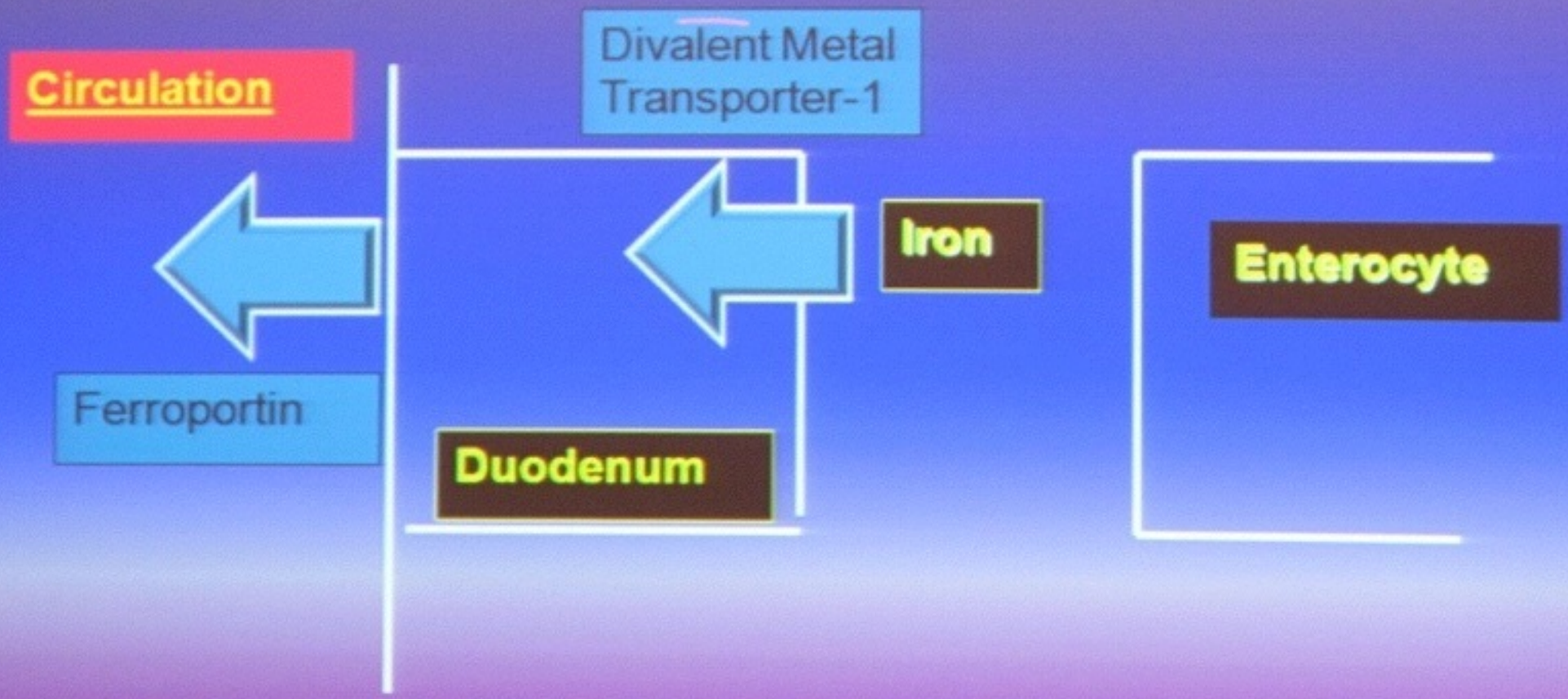
Iron in the Critically Ill

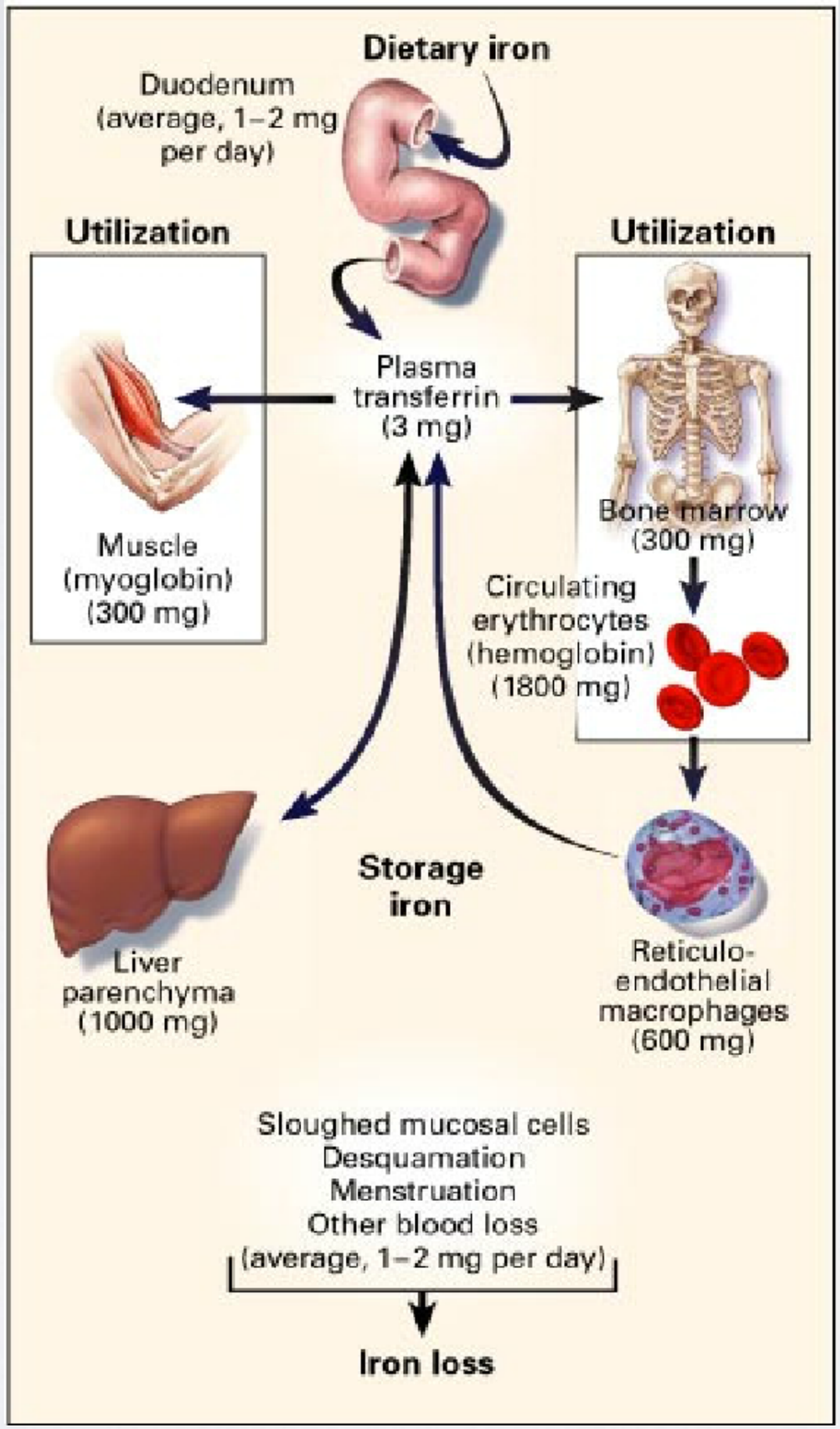
ROLE OF IRON

- Iron is essential for O_2 transport by Hb and myoglobin.
- In physiologic conditions, Hb contains 80 % of the total body iron stores.
- Iron is used primarily for heme biosynthesis in erythroid cells.
- Erythroids cells take up iron from transferrin, which binds to the transferrin receptor on the cell surface.

Intestinal Iron Absorption

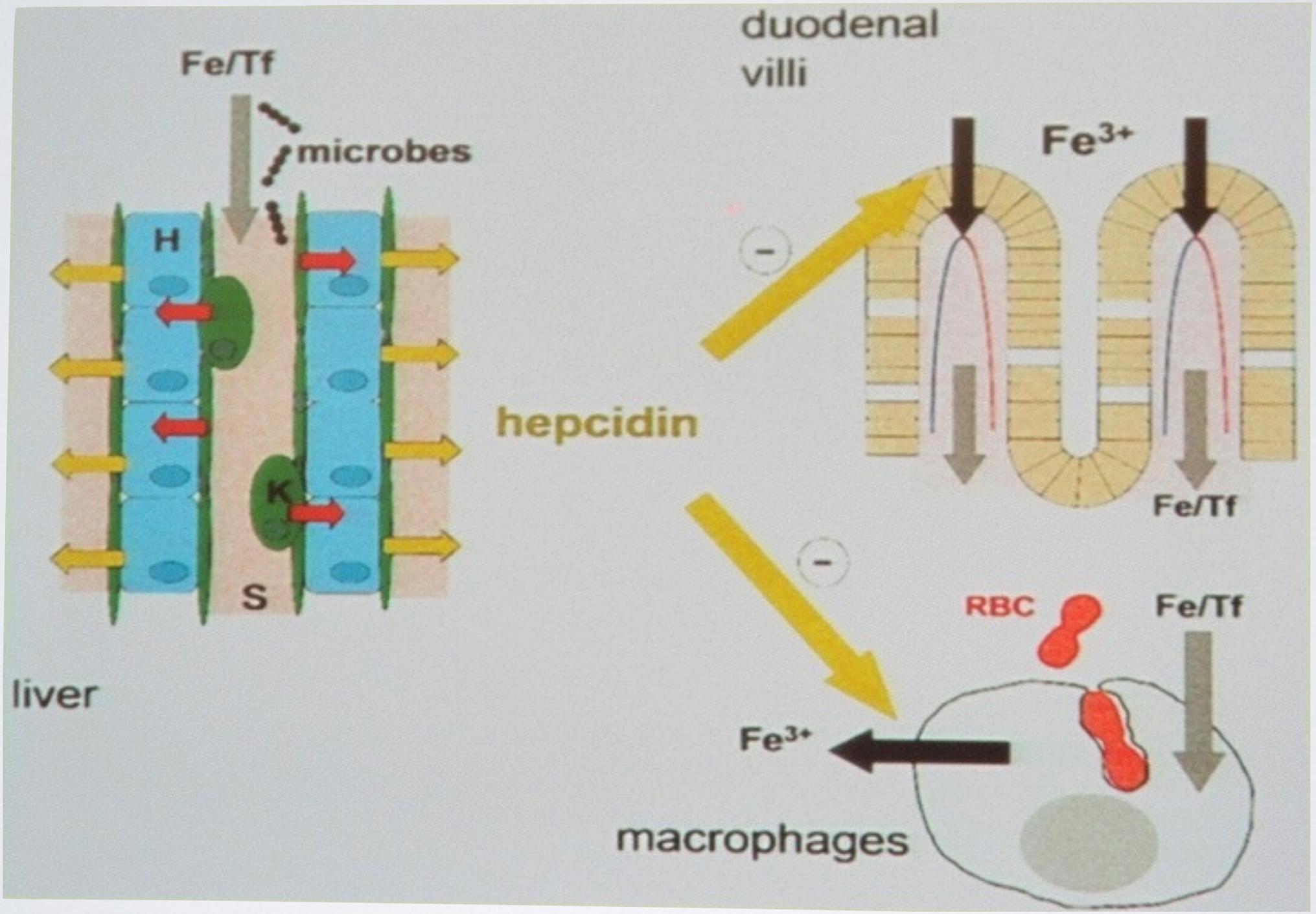
Gunshin H et al. Nature 1997; 388: 482-488.





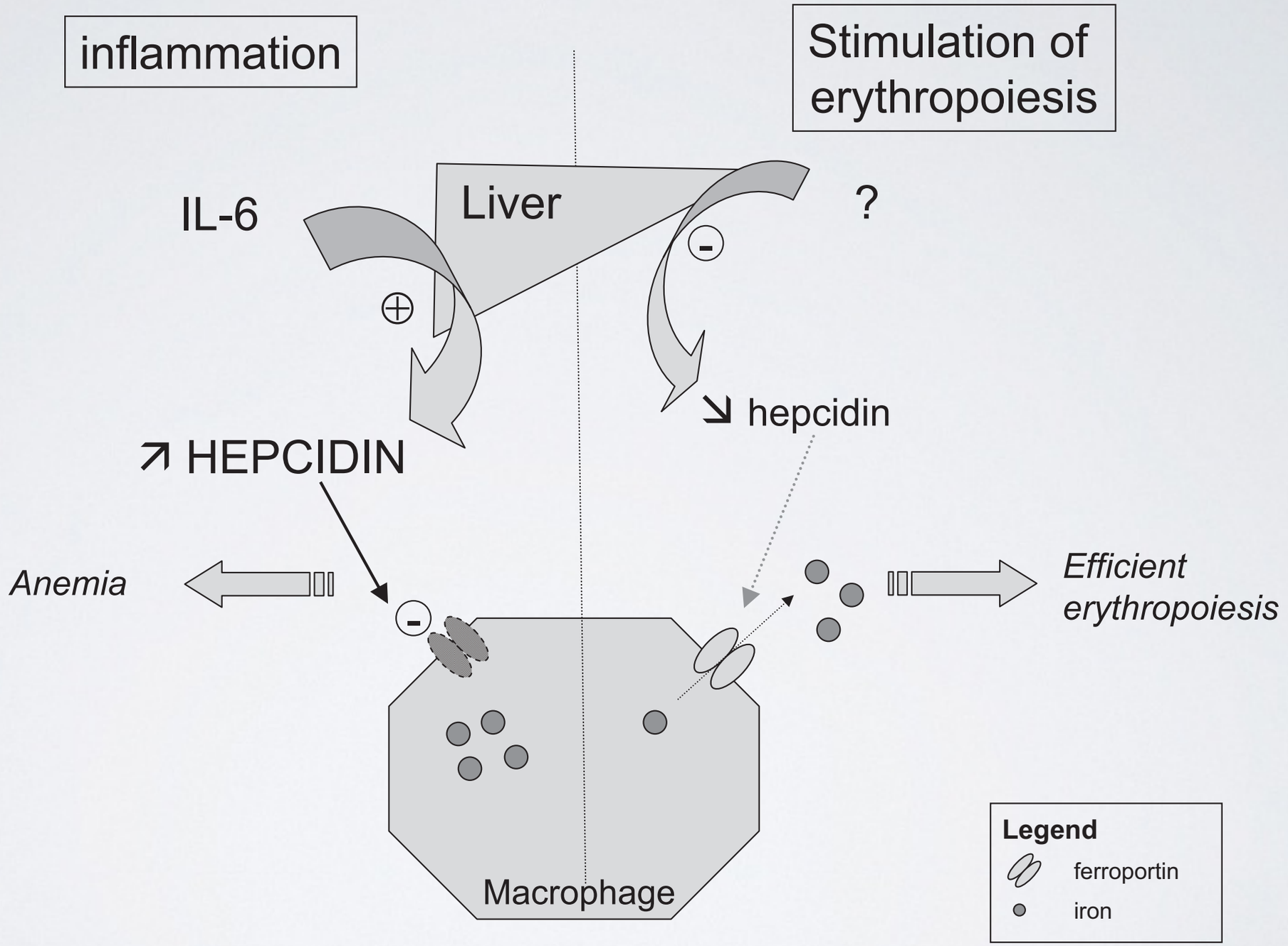
N Engl J Med 1999; 341:1986-1995

Hepcidin-regulator of iron intestinal absorption



Blood 2003;102:783-788

Hepcidin-regulator of iron intestinal absorption



Crit Care Med 2008 Vol. 36, No. 8

Pathophysiology of Iron metabolism

- Role of proinflammatory cytokines
  - TNF-α, IL-1β, IL6 increase iron storage by reticuloendothelial system
  - Induces the transcription of ferritin
- Limits availability for erythrocytes

Hypoferraemia and hyperferritinaemia in inflammatory states
Decrease serum Iron levels

Eur J Clin Invest. 1998;28:520-527

Blood 1996;87:2525-2537

Pathophysiology of Iron Metabolism

Aim

Deprive bacteria of iron

Iron-conclusions

- Iron status rapidly altered in critically ill
- These alterations persist during course of disease
  - Associated with decreased erythropoiesis
- Iron is an essential component of bacterial growth
- Iron sequestration during inflammation could represent a defense mechanism
- Iron administration could therefore, in theory, increase the host susceptibility for bacterial infections
  - Animal models show that injection of iron leads to increased susceptibility to bacterial infection
- Further studies are needed before treating with iron supplements in critically ill

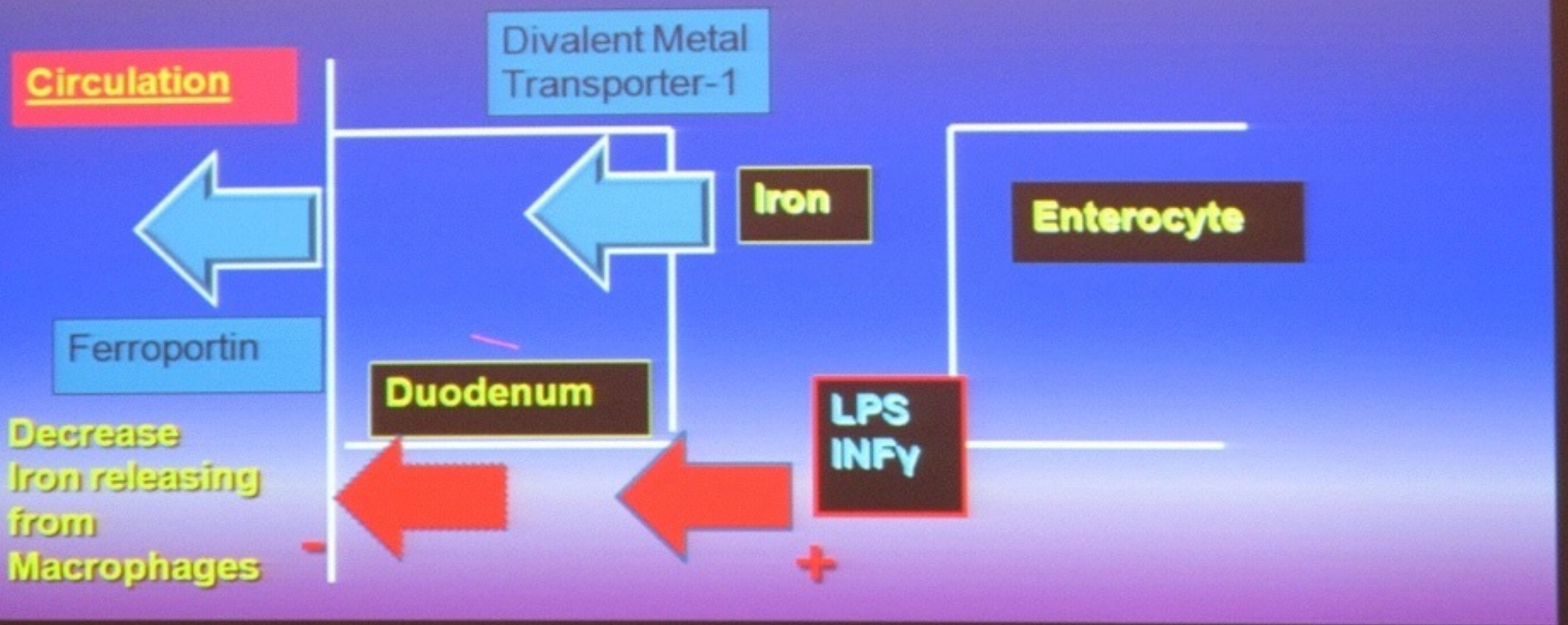
IRON

We need it

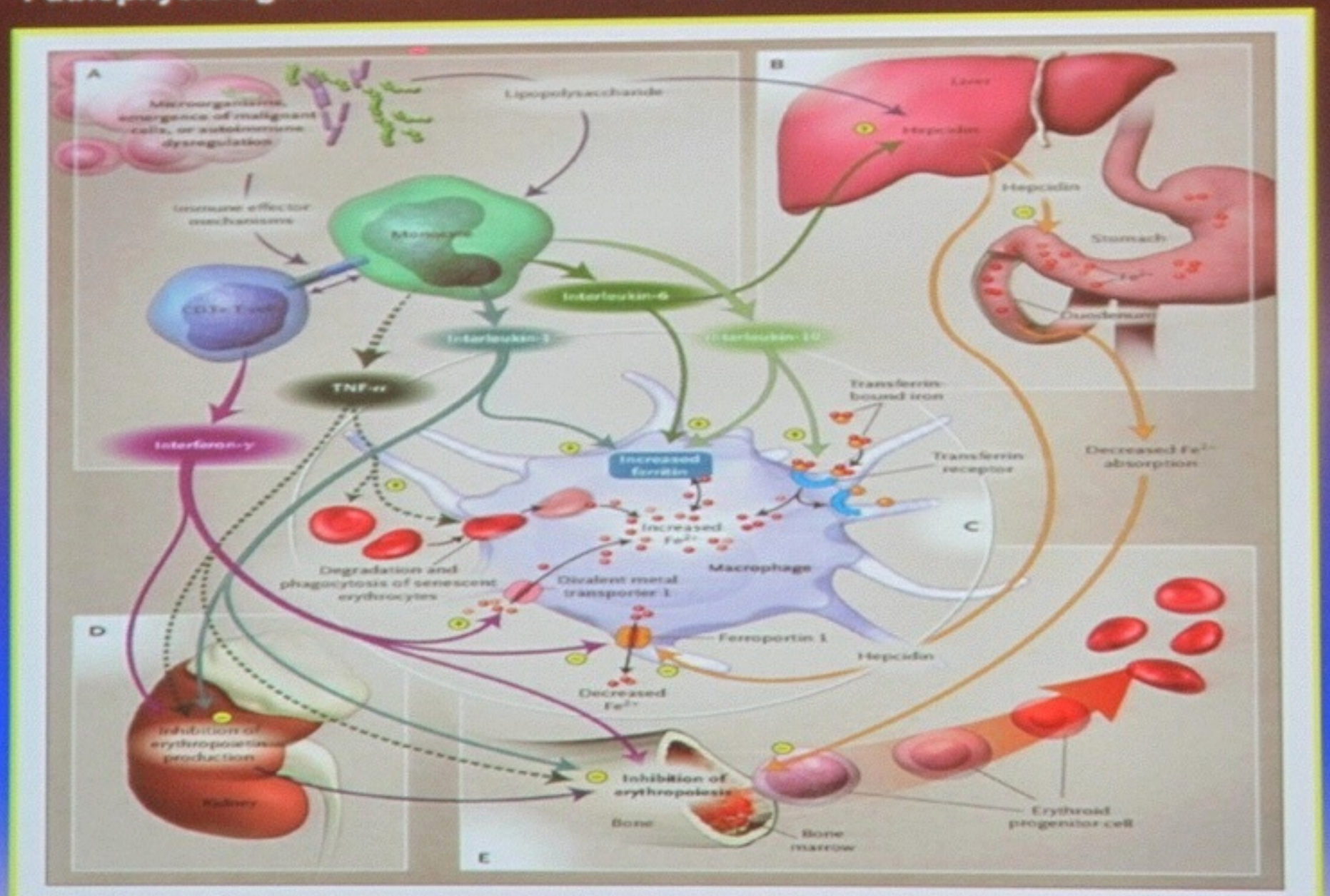
They also need it

Intestinal Iron Absorption during Inflammation

Ludwiczek S et al. Blood 2003; 101: 4148-4154



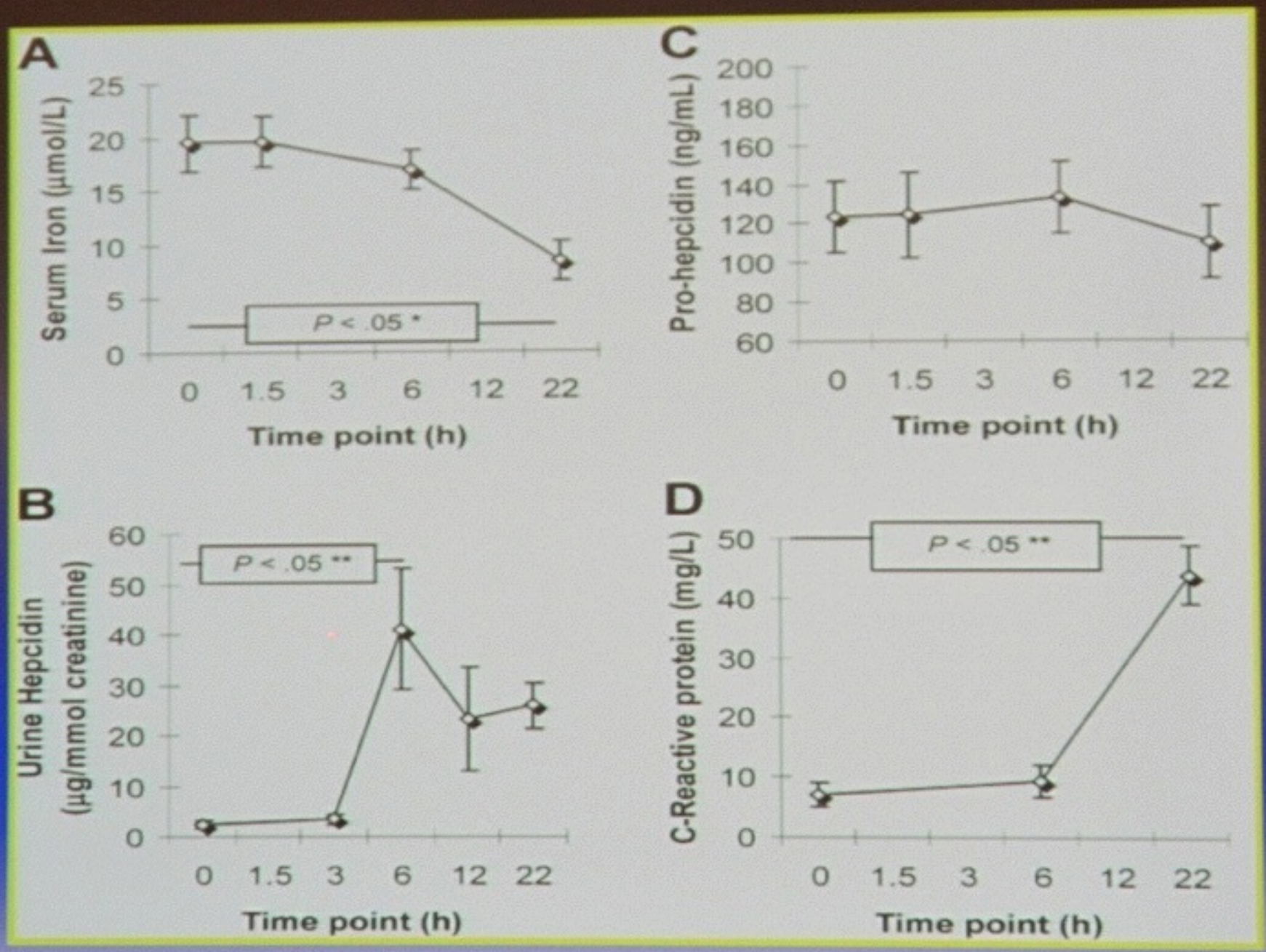
Pathophysiological Mechanisms Underlying Anemia of Chronic Disease



Weiss, G. et al. N Engl J Med 2005;352:1011-1023

The NEW ENGLAND JOURNAL of MEDICINE

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Kemna, E. et al. Blood 2005;106:1864-1866

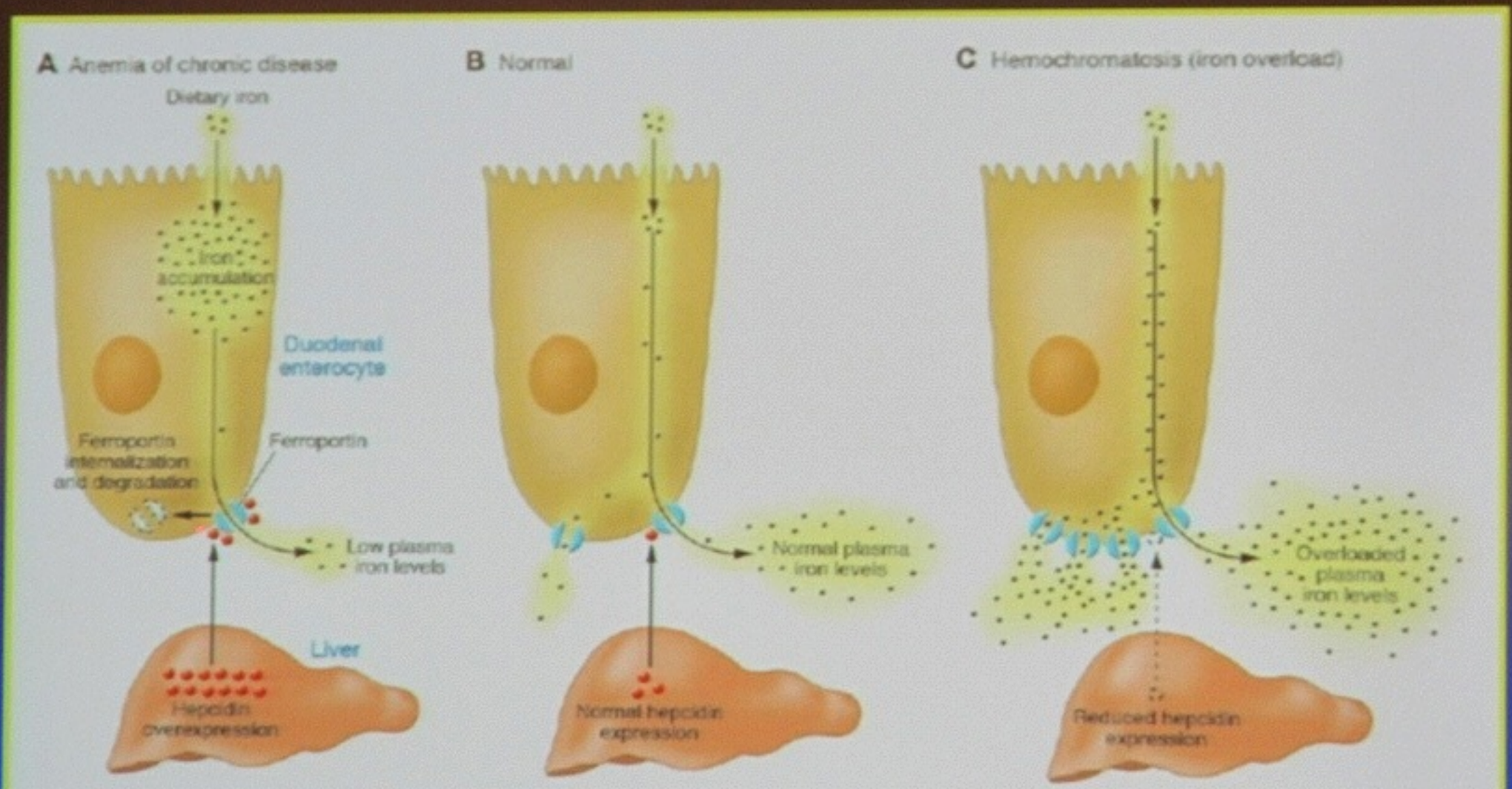


Figure 1

Hepcidin-mediated regulation of iron homeostasis. (**A**) Increased hepcidin expression by the liver results from inflammatory stimuli. High levels of hepcidin in the bloodstream result in the internalization and degradation of the iron exporter ferroportin. Loss of cell surface ferroportin results in macrophage iron loading, low plasma iron levels, and decreased erythropoiesis due to decreased transferrin-bound iron. The decreased erythropoiesis gives rise to the anemia of chronic disease. (**B**) Normal hepcidin levels, in response to iron demand, regulate the level of iron import into plasma, normal transferrin saturation, and normal levels of erythropoiesis. (**C**) Hemochromatosis, or iron overload, results from insufficient hepcidin levels, causing increased iron import into plasma, high transferrin saturation, and excess iron deposition in the liver.

De Domenico et al. JCI 2007; 117 : 1755- 1758

IRON STATUS IN CRITICALLY ILL

	Normal values	Non-septic (n=62)	Septic (n=33)	p value
Reticulocytes		58 [48-77]	42 [29-61]	0.028
Iron (µg/dL)	50-150	50 [28-75]	21 [15-34]	< 0.001
Ferritin (mg/dL)	30-350	204 [78-354]	432 [184-773]	0.002
Transferrin (mg/dL)	200-360	214 [173- 247]	169 [121-215]	0.003
R tsf (mg/dL)	0.2-0.5	0.26 [0.21-0.36]	0.25 [0.21-0.36]	0.95
Sat Tsf (%)	15-55	19 [11-25]	11 [7-15]	0.004

Reversal of Vitamin K antagonists in the bleeding patient

Vitamin K antagonists
an epidemiological problem

- 2% of population prescribed VKA
- UK : haemorrhage while taking VKA is one of principle reasons of drug related admission to hospital
- Under-estimation of hemorrhagic events
  - Risk is 4-13%
  - Anticoagulant-associated ICH is X5 in the 90s

Pirmochamed BMJ 2004
Budnitz D et al NEJM 2011
Flaherty M Neurology 2007

Vitamin K antagonists decreases thrombotic risks

- Cardiac valves- Stroke
  - nothing: 4% / patient-year
  - aspirin: 2.2% / patient-year
  - **VKA: 1% / patient-year**
- Atrial fibrillation - Stroke
  - nothing: 4% / patient-year
- DVT and pulmonary embolism

Guidelines for Reversal

- Rapid reversal only if severe haemorrhage
  - **Antidote** - as soon as diagnosis confirmed
    → restore the missing factors (II, VII, IX, X) by using prothrombin complex concentrates (PCC)
    PCC (4 factors) is superior to FFP
  - **Early correction**
    - Time to normalise
    - **60** ml of PPC = **2000** mL of FFP
    - TRALI (antibodies)
    - But factor VII 1/2 life = 5-6 hrs
  - **Delayed correction: Vit K**
    - 6-8 hrs to be effective
- Essential to measure INR after 6 hrs

Rapid reversal only if severe haemorrhage

- What is a severe haemorrhage?
  - **Shock**
  - **RBC transfusion**
  - **Localisation : deep muscles, digestive tract, lung and brain** - risk from 1% to 17%, risk x 10
    - VKA + cerebral haemorrhage = progression of bleeding in 50% of cases

Guidelines for Reversal

Guideline	Country	Year	Reference
PCC 50 IU/kg + Vit K 5-10 mg IV	UK	2006	BJH 2006 132;277-85
PCC 40 IU/kg + Vit K 5-10 mg IV	France	2008	AFSSAPS

PCC 20-50 IU/kg + Vit K 5-10 mg

In real life

- France 2001 : treatment of severe haemorrhages (n=198)

  associated PCC = 29%

- Doctors decrease PCC dose: 15 IU/Kg instead of 20–40 IU/Kg[1]

- Each time we search, each time we found:
  Sweden, United Kingdom. 1992, 1998, 2002, 2007, 2009...

Gap between guidelines and reality

[1] Sié P. *Urgence Pratique* 2002

Why?

Our perception of risk is not only about probability

- Education:
  - Chronic treatment is justified
  - It’s not so easy to change the way of thinking
  - Thrombosis before haemorrhage then haemorrhage first

- If you ask for specialist advice: cardiologists, neurologists, haematologists
  - You will get…… thrombosis-related specialist advice

28-day mortality in metanalysis, Dentali, 2011
Thrombosis 3‰ vs Hemorrhage 10%

- Real haemorrhagic risk evaluation is often missing

Why?

- Confusion between normal INR and therapeutic INR
  - 50 to 70% of patients with haemorrhagic stroke have therapeutic INR[1,2]
- ***"You wouldn't say that if you had seen a valve thrombosis"***

  It's precisely because this event has a very low probability that we can say that...

  With a normal coagulation in 1992:
  risk is 1.8%/patient year = 0.005% per day

- How our memory works and how experience is transmitted
- Death is more easily accepted if due to a useful treatment

1. Rosand J, *Arch Intern Med* 2004 ; 2. Koo S., *Arch Intern Med*, 2004

What is the problem?

These patients must be considered like any patient with a life-threatening haemorrhage

1. Diagnosis of severe haemorrhage

2. No loss of time: quickly reverse anticoagulation, improve ease of use

3. No loss of opportunity: surgery as fast as for non-anticoagulated patient

What is the “The French solution”?

AFSSAPS, April 2008

- Improve ease of use
  - availability: room temperature storage in emergency department
  - no loss of time waiting for admission INR
  - faster administration time
  - probabilistic dose of PCC = 1 dose

    25 IU/Kg (1 mL/Kg) with an immediate INR control
- Don’t forget vitamin K (10 mg) and INR control 6 hours later

Improved ease of use

Studies for rapid antagonism

- Warfarin:
  - **Injection: 17 min + time for control: 30 min = 47 min[1]**
  - Injection + control: 10 min (n=17)[2]
  - Injection: 10 min + control: 20 min = 30 min (n=42)[3]
  - Injections (2 to 40 mL/min) = no difference (n=43)[4]
- Phenprocoumon:
  - Injection: 6 min + control: 10 min = 16 min (n=8)[5]

1. **Guidelines** ; 2. Yasaka M, *Thromb Res*. 2002 ; 3. Preston FE, *Br J Haematol*. 2002 ; 4. Pabinger, *Ann Hematol*. 2010 ; 5. Lorenz R, *Blood Coagul Fibrinolysis* 2007 ;

“The French solution” in severe haemorrhage

PRISE EN CHARGE HOSPITALIERE D’UNE HEMORRAGIE GRAVE : OBJECTIF : INR < 1,5

Arrêt des AVK et mesure de l’INR en urgence

Si INR disponible :
Administration de CCP* à dose adaptée à l’INR, selon les RCP.

Si INR non disponible :
Administration de CCP* 25 U/kg (soit 1 ml/kg).

Et Vitamine K 10 mg (1 ampoule adulte) - Privilégier la voie per os.

Contrôle INR à 30min

Si INR > 1.5: nouvelle dose de CCP selon RCP
Contrôle INR à 6 – 8h

AFSSAPS & HAS, 2008

"The French solution" in severe haemorrhage

PRISE EN CHARGE HOSPITALIERE D'UNE HEMORRAGIE **Target INR ≤1.5**

Arrêt des AVK et mesure de l'INR en urgence

Available INR

Administration de CCP* à dose adaptée à l'INR, selon les RCP.

Si INR non disponible :
Administration de CCP* 25 U/kg (soit 1 ml/kg).

Et Vitamine K 10 mg (1 ampoule adulte) - Privilégier la voie per os.

Contrôle INR à 30min

Si INR > 1.5: nouvelle dose de CCP selon RCP
Contrôle INR à 6 – 8h

AFSSAPS & HAS, 2008

"The French solution" in severe haemorrhage

PRISE EN CHARGE HOSPITALIERE D'UNE HEMORRAGIE

Target INR ≤1.5

Arrêt des AVK et mesure de l'INR en urgence

Available INR

Administration de CCP* à dose adaptée à l'INR, selon les RCP.

Non available INR

PCC 25 IU/Kg, 1 mL/Kg

Et Vitamine K 10 mg (1 ampoule adulte) - Privilégier la voie per os.

Contrôle INR à 30min

Si INR > 1.5: nouvelle dose de CCP selon RCP
Contrôle INR à 6 – 8h

AFSSAPS & HAS, 2008

"The French solution" in severe haemorrhage

PRISE EN CHARGE HOSPITALIERE D'UNE HEMORRAGIE

Target INR ≤1.5

Arrêt des AVK et mesure de l'INR en urgence

Available INR

Administration de CCP* à dose adaptée à l'INR, selon les RCP.

Non available INR

PCC 25 IU/Kg, 1 mL/Kg

Vitamin K 10 mg e adulte) - Privilégier la voie per os.

Control INR

Si INR > 1.5: nouvelle dose de CCP selon RCP
Contrôle INR à 6 – 8h

AFSSAPS & HAS, 2008

"The French solution" in severe haemorrhage

PRISE EN CHARGE HOSPITALIERE D'UNE HEMORRAGIE

Target INR ≤1.5

Arrêt des AVK et mesure de l'INR en urgence

Available INR

Administration de CCP* à dose adaptée à l'INR, selon les RCP.

Non available INR

PCC 25 IU/Kg, 1 mL/Kg

Vitamin K 10 mg e adulte) - Privilégier la voie per os.

Control INR

If INR >1.5 : new dose adapted to control INR

AFSSAPS & HAS, 2008

Conclusions (1/2)

VKA reversal :
Not "New", just focuses on the situation

- 1 treatment: PCC and vitamin K
- 1 dose (1 mL/Kg)
- 1 rapid injection
- 1 control after treatment

PCC 25 IU/Kg + vitamin K 10 mg

Conclusions (2/2)

Antidote

- Stopping haemorrhages quickly will save lives
- Ultra rapid reversal is possible and necessary
- There is no reason for delayed surgery
- Improve education, local recommendations, …


"That's all Folks!"