

Controvèrsies en el maneig de la sèpsia greu

Nous estudis PROCESS i ARISE. Rivers encara és viu?

Ricard Ferrer

Intensive Care Department

Mutua Terrassa University Hospital

Barcelona. SPAIN

ciberes



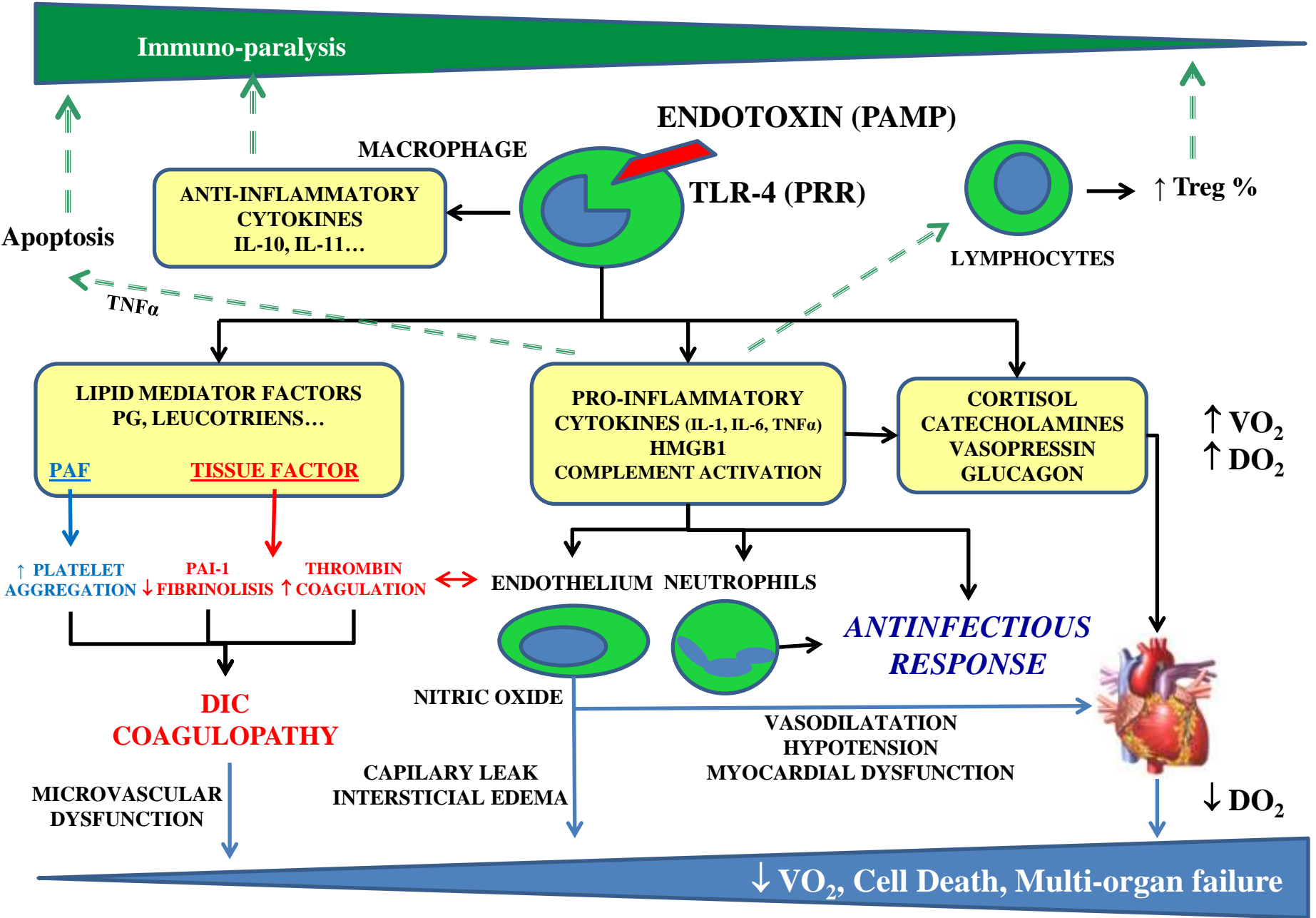
Mútua Terrassa



UNIVERSITAT DE BARCELONA

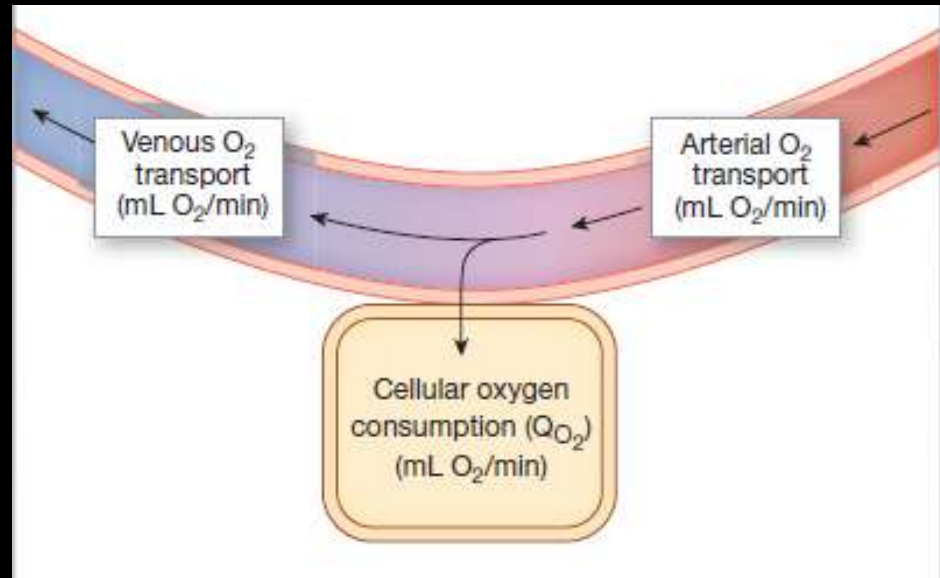


EDUSEPSIS



Tissue dysoxia

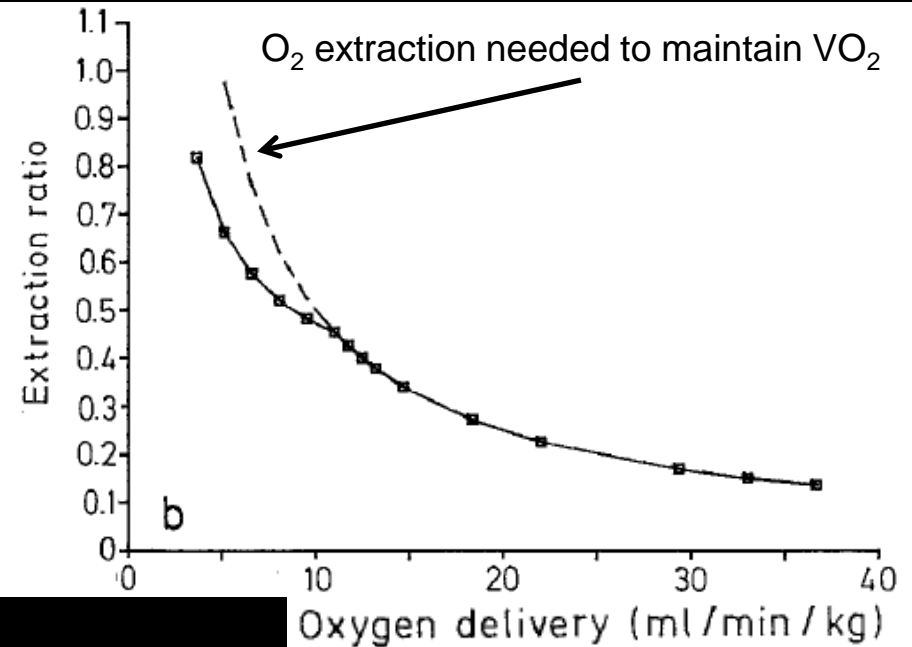
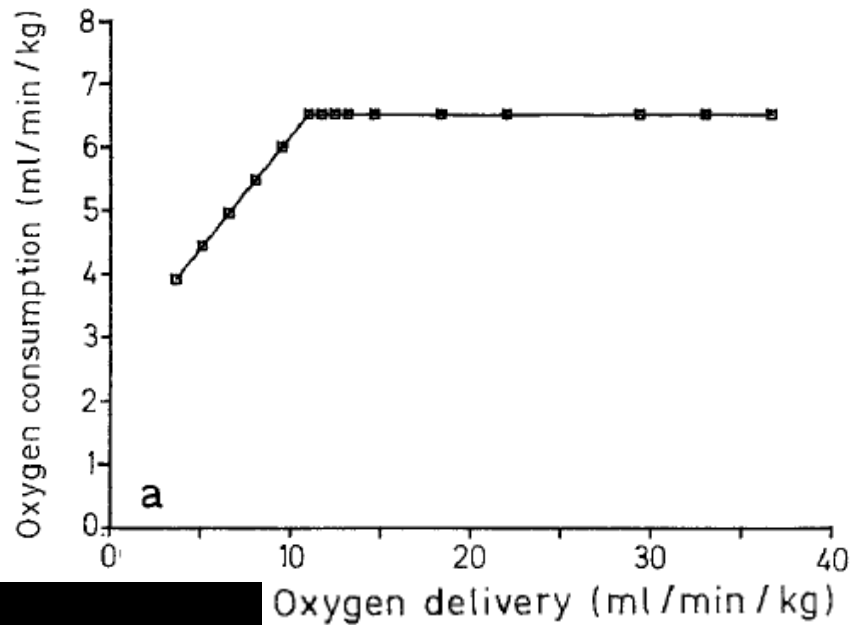
- **Oxygen Consumption ($\dot{V}O_2$):** O_2 extracted by the tissues.



- The rate (ml/min) at which O_2 dissociates from hemoglobin in the microcirculation and moves into the tissues.

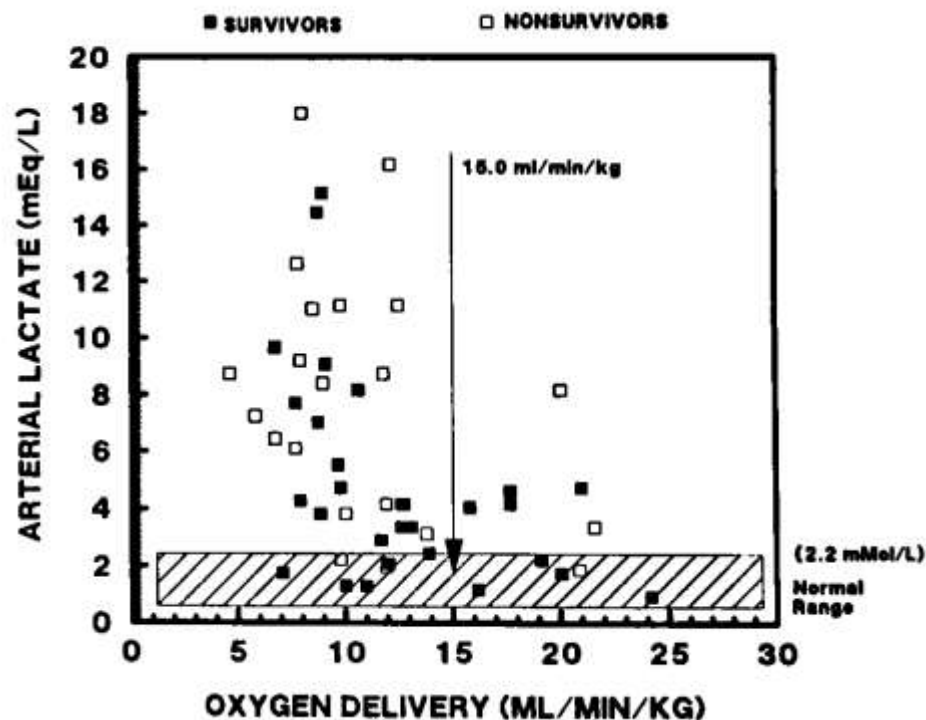
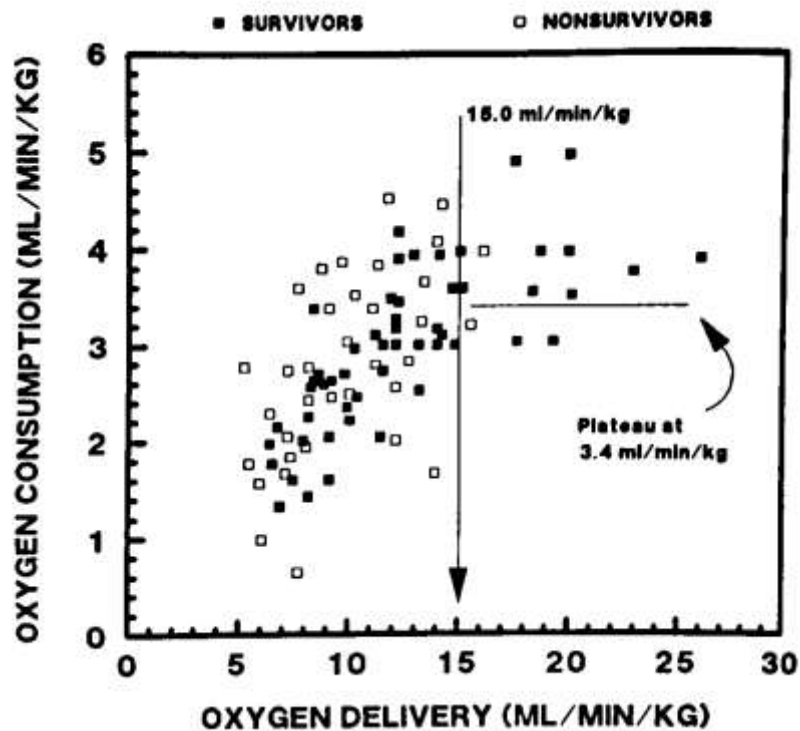
The concept of a critical oxygen delivery

P. T. Schumacker¹ and S. M. Cain²

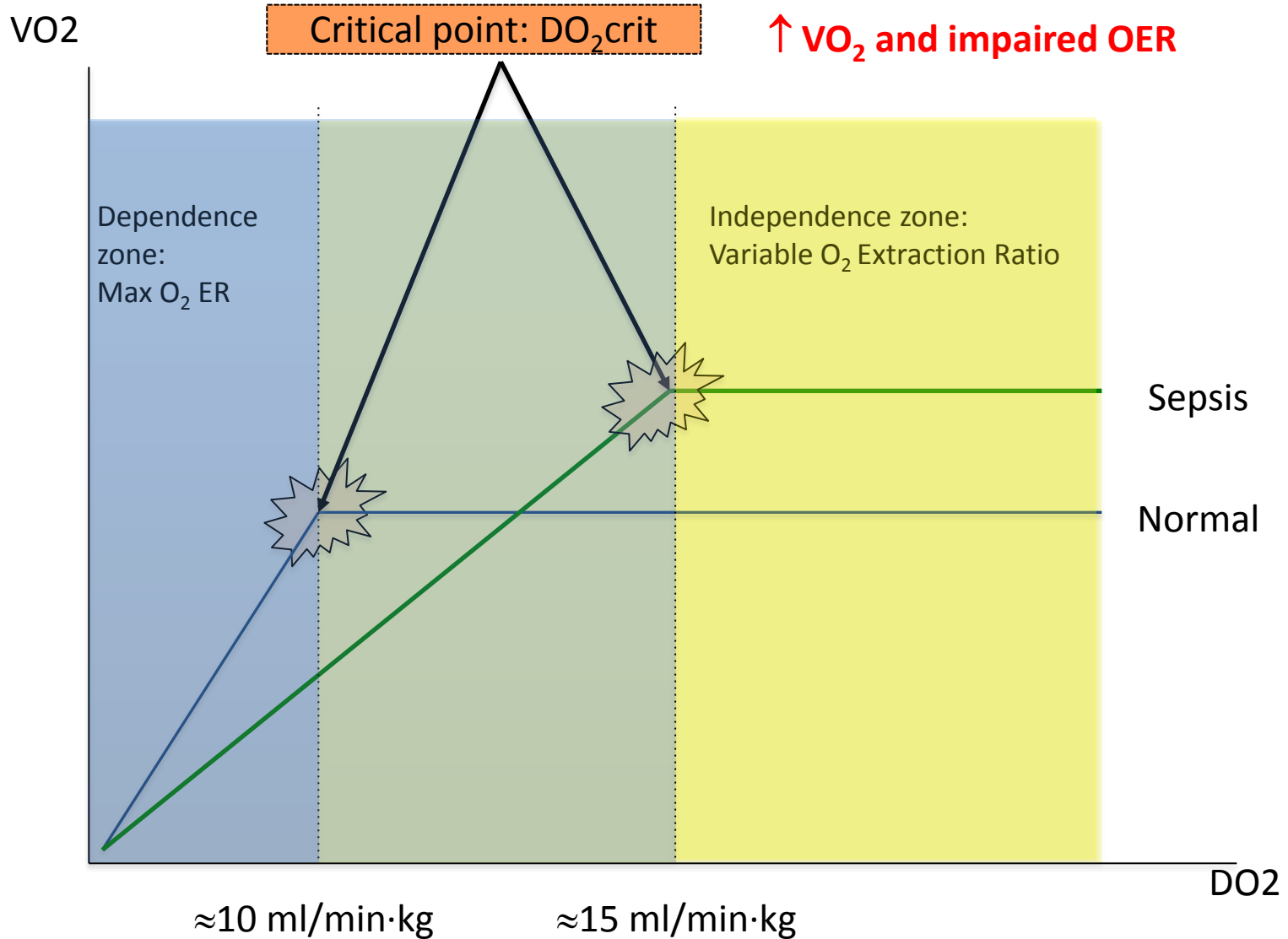


Oxygen consumption in sepsis and septic shock

JAMES TUCHSCHMIDT, MD; DANIEL OBLITAS, MD; JEFFREY C. FRIED, MD

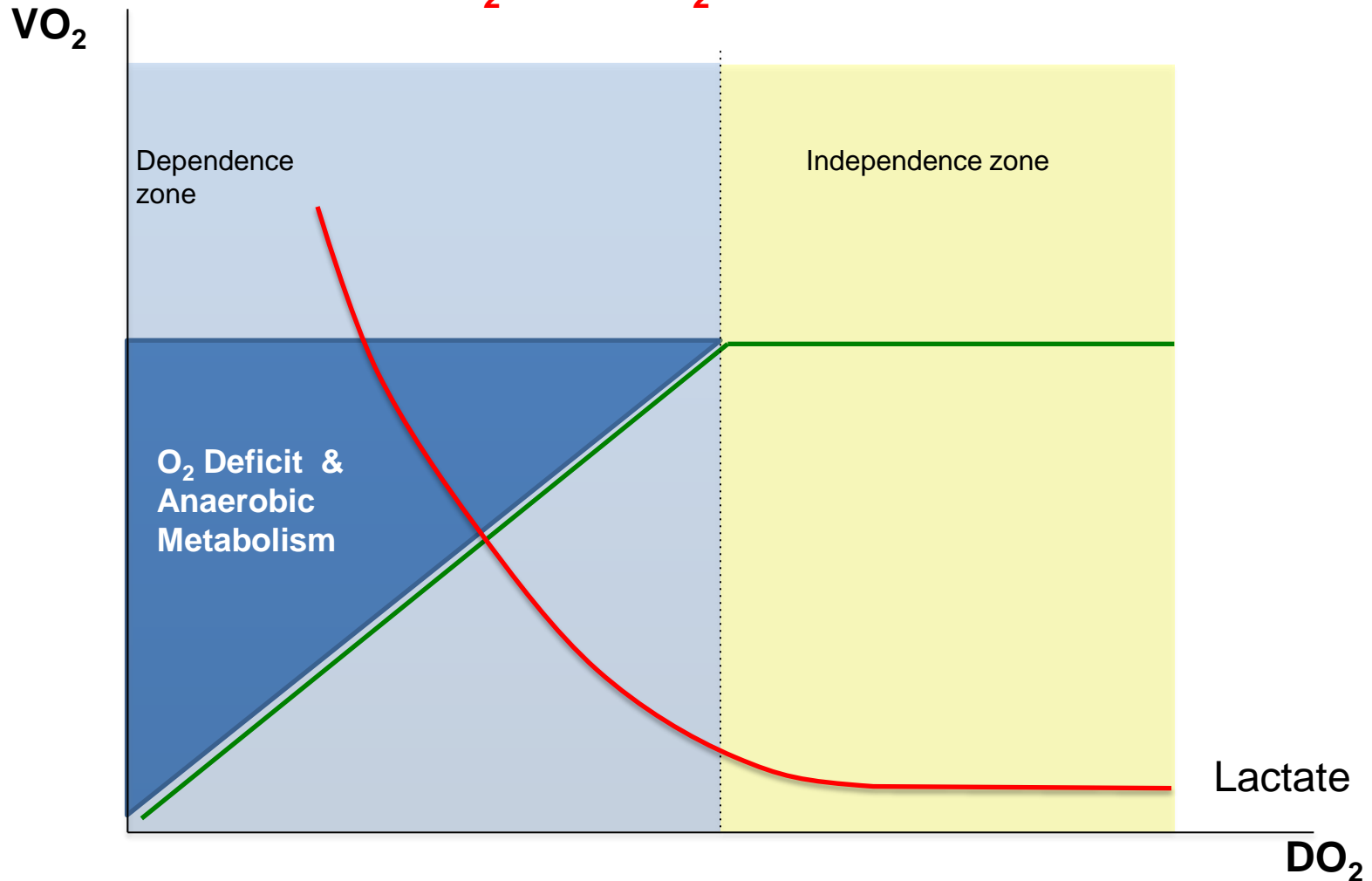


The biphasic $\text{VO}_2 - \text{DO}_2$ model



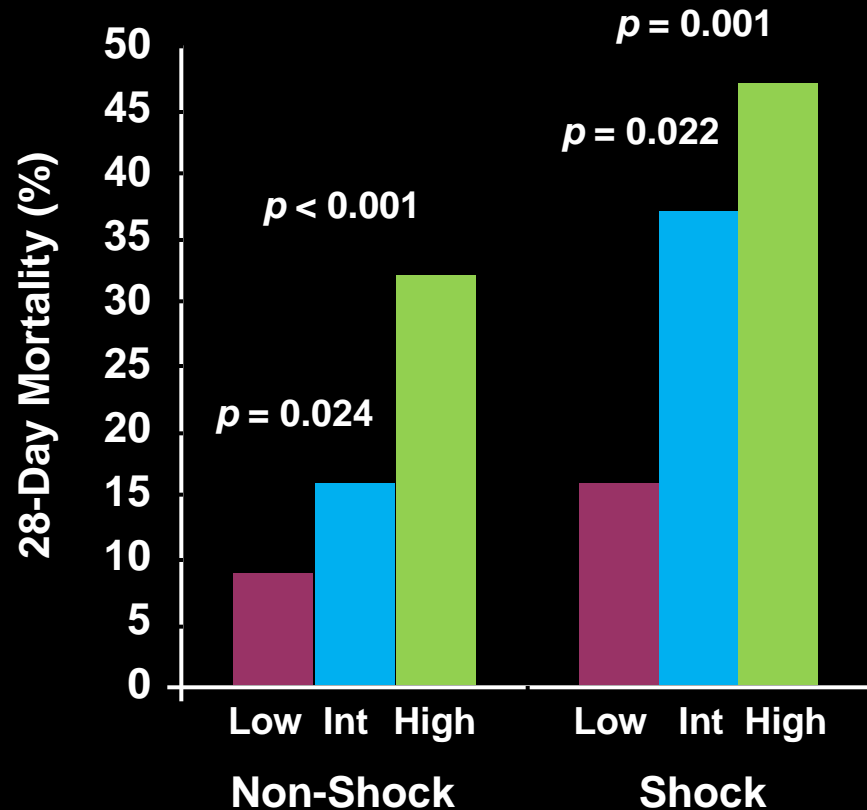
$VO_2 - DO_2$ model: O_2 Debt

$$O_2 \text{ Debt} = O_2 \text{ Deficit} \times \text{Time}$$



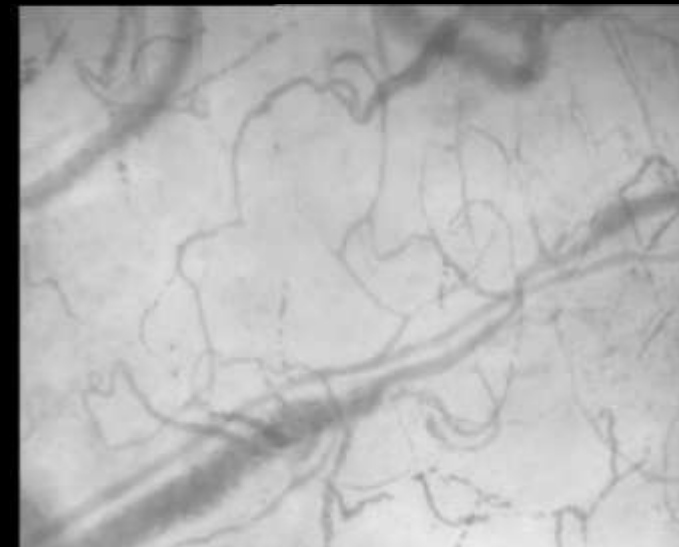
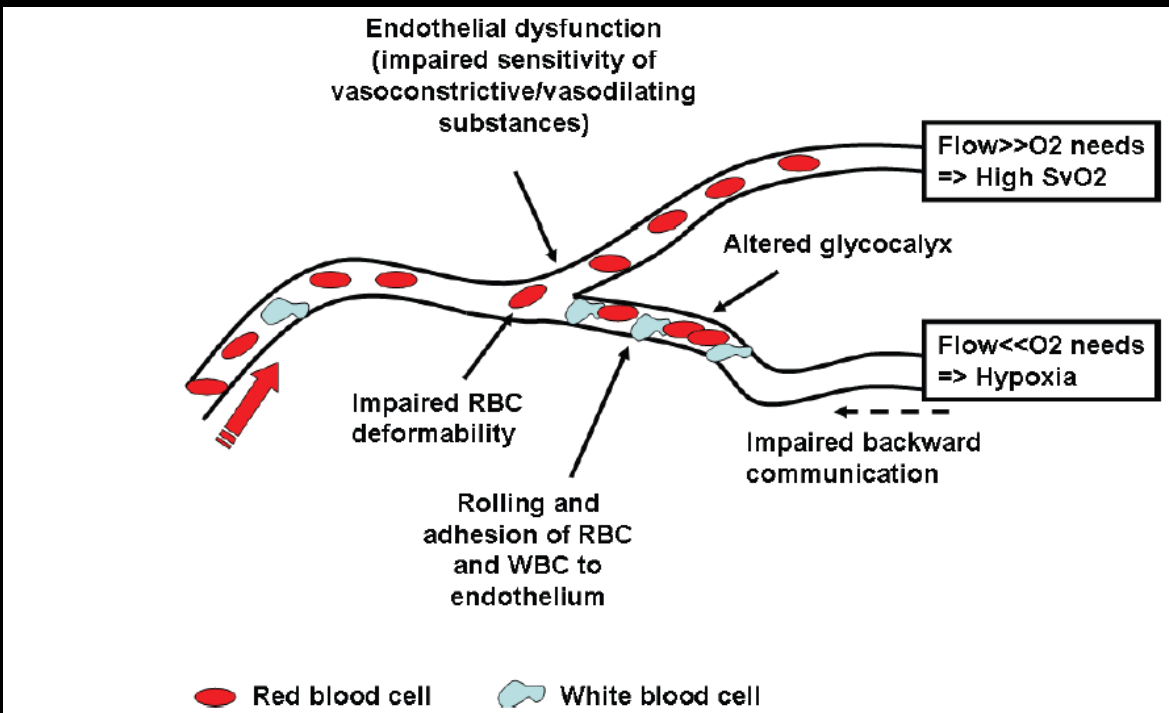
Serum Lactate and Mortality in Severe Sepsis

High initial serum lactate associated with \uparrow mortality regardless of presence of shock (hypotension despite fluid resuscitation).



VO₂ and alteration of microvascular flow

Principal mechanisms implicated in the development of microcirculatory alterations



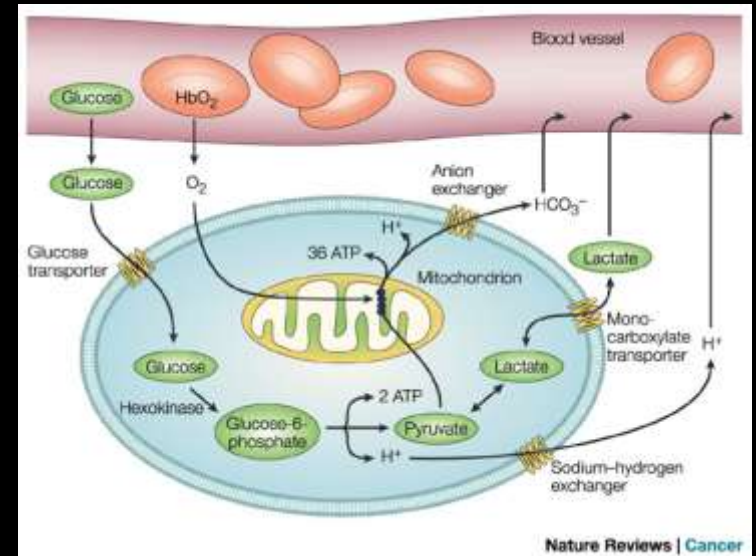
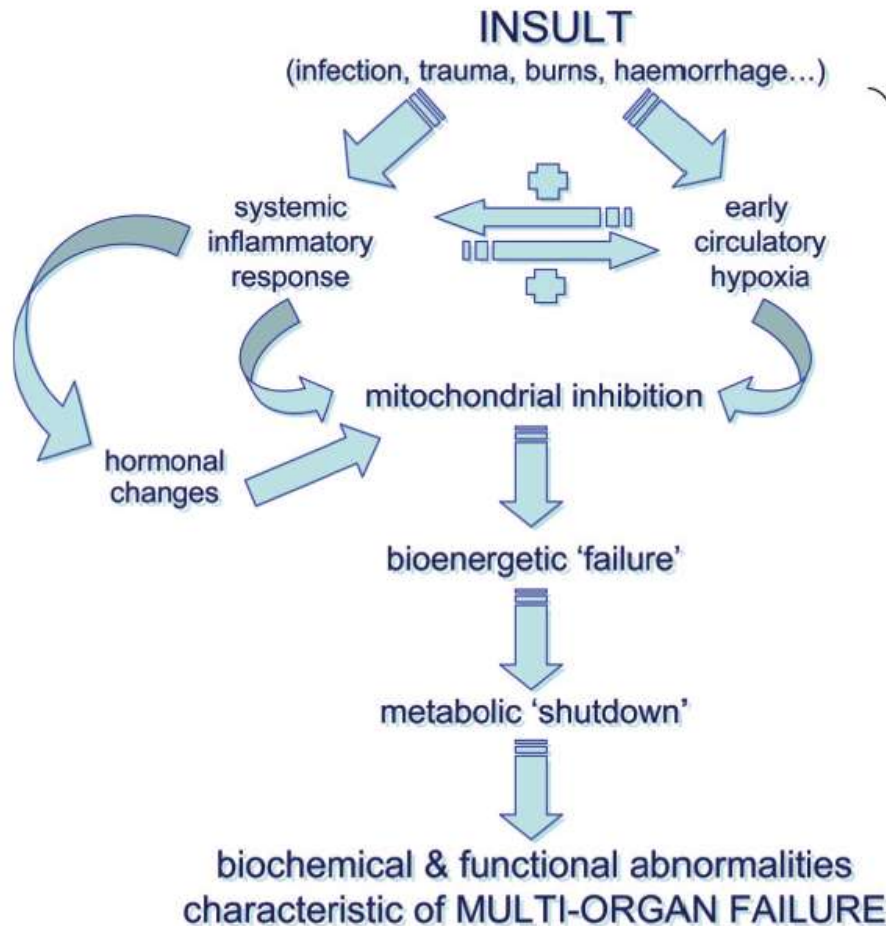
↓ Capillary density
↑ number of stopped-flow and
intermittent-flow capillaries

↓ surface for O₂ exchange

Metabolic failure

Mervyn Singer, MD

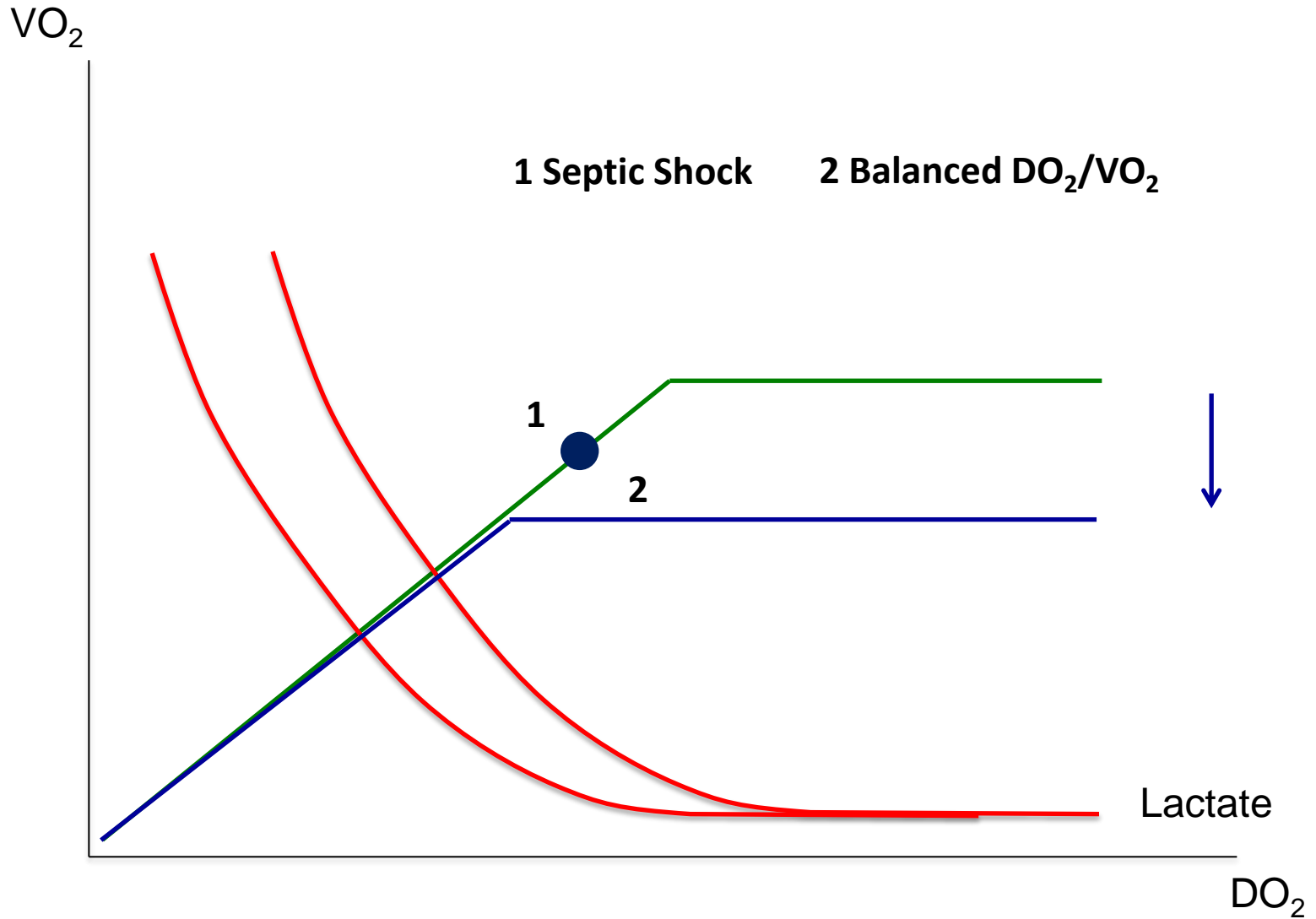
Crit Care Med 2005 Vol. 33, No. 12



Treatment strategies: balanced DO_2/VO_2



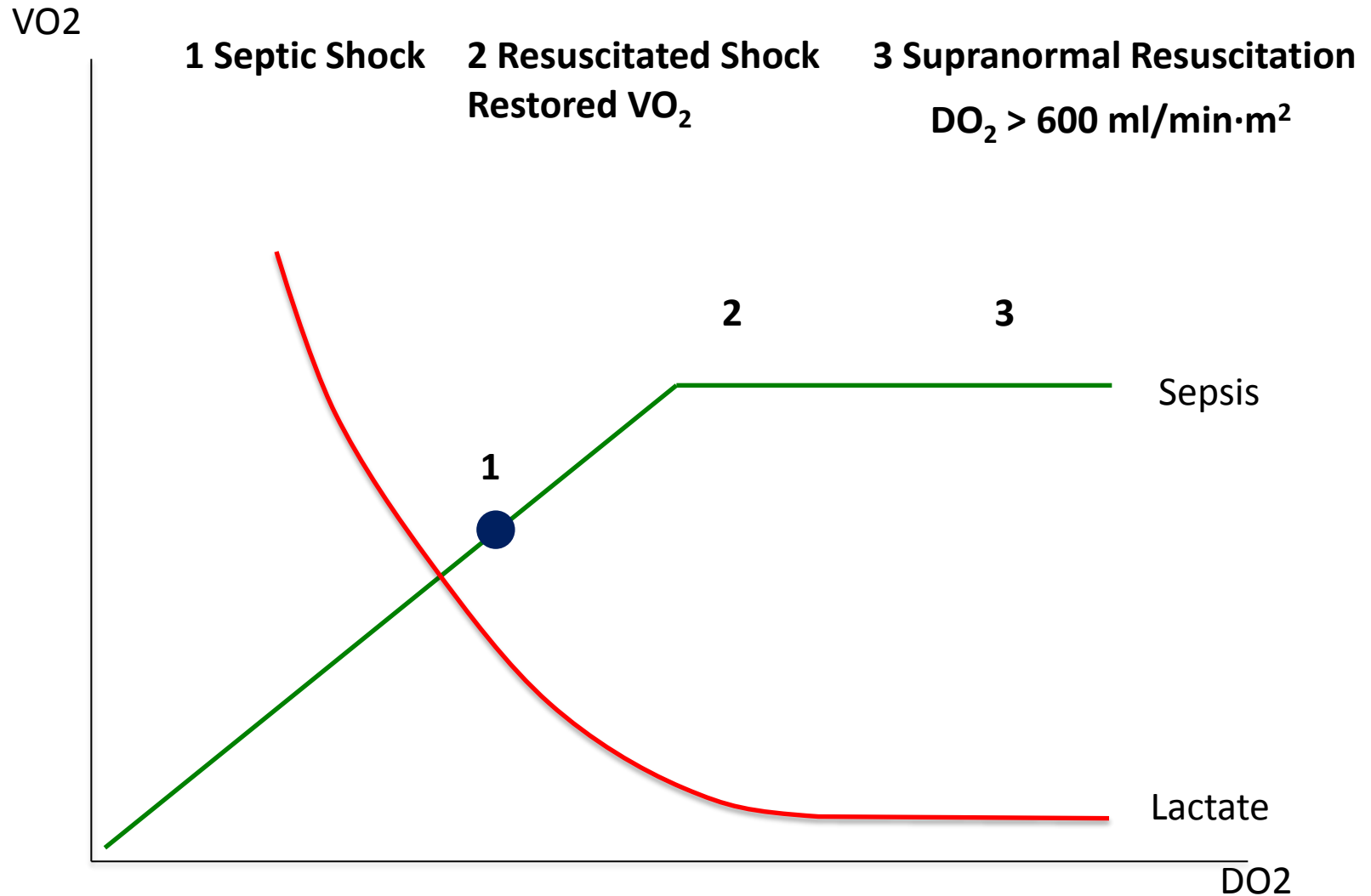
Decrease VO_2



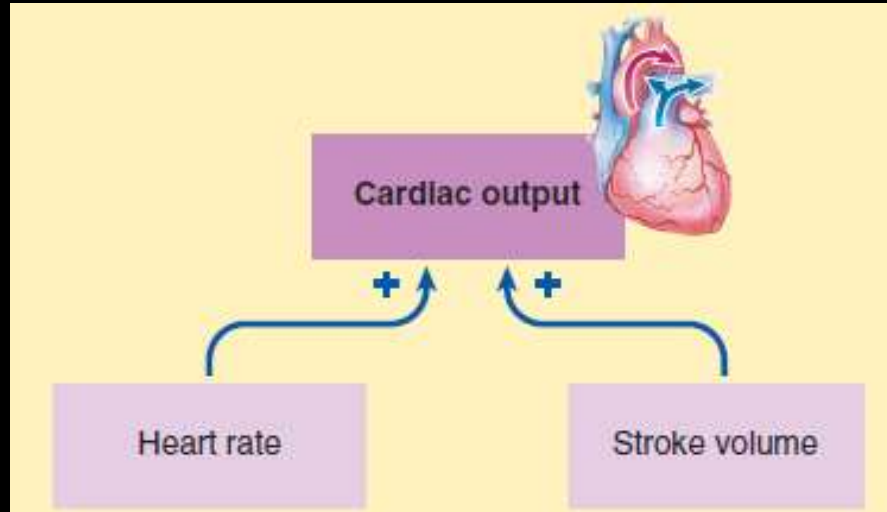
Decrease VO_2

- Analgesia
- Normotermia (or hipotermia)
- Mechanical Ventilation.
- Infection control: Adequate empirical antibiotics and Source Control.
- Titrate minimum dose of Thermogenic drugs like inotropes.

Increase DO_2



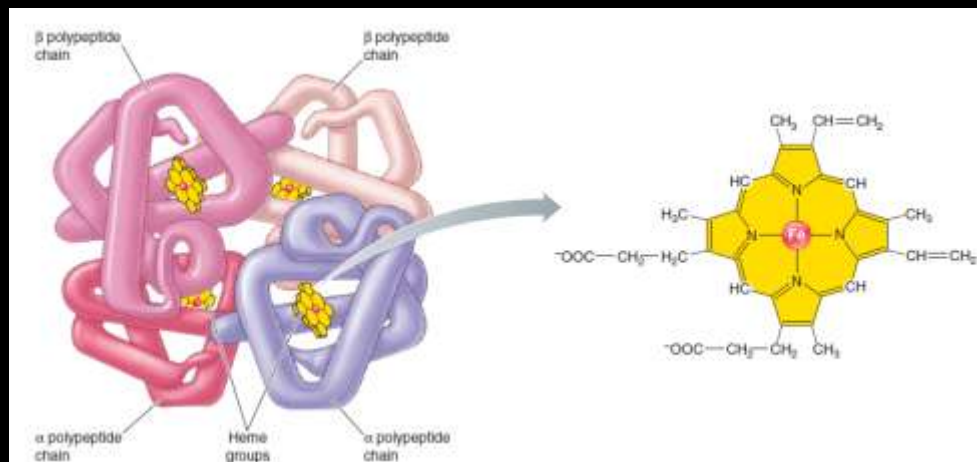
$$DO_2 = CO \times CaO_2$$



TREATMENTS

Fluids
Inotropes
Vasopressors

$$CaO_2 \approx Hb \times 1.34 \times SaO_2 / 100$$

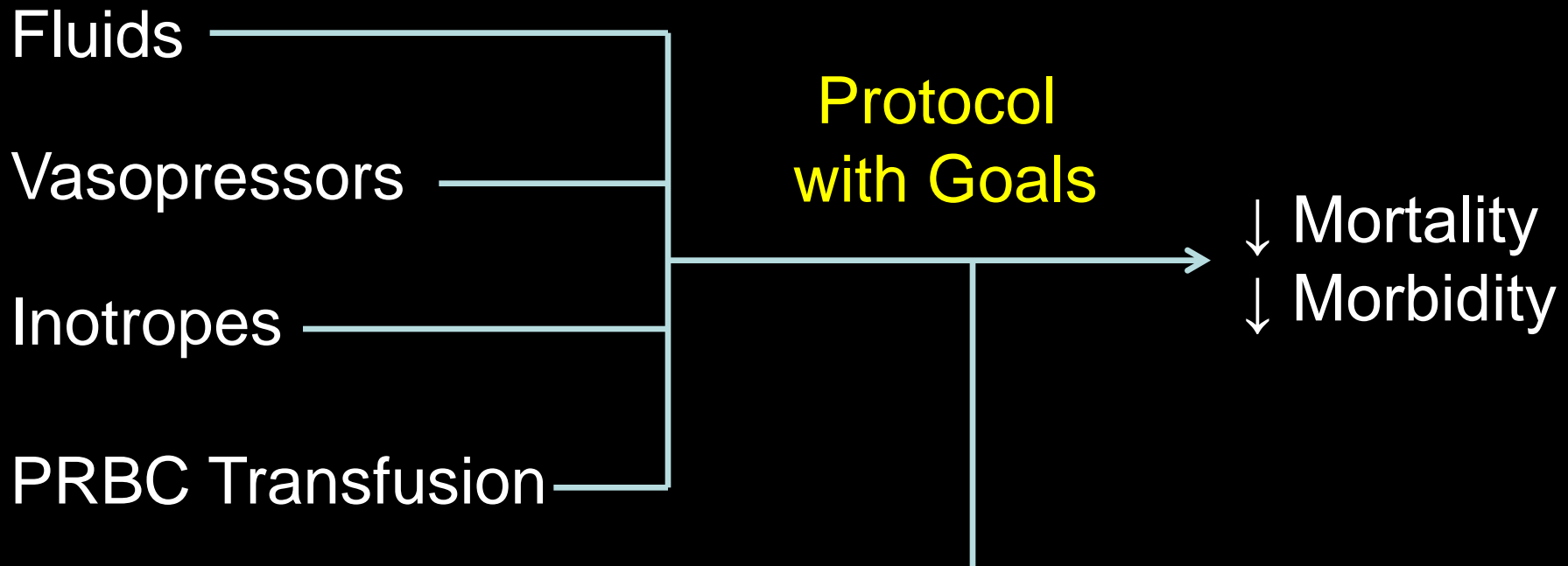


O_2
PRBC

End-Points of Resuscitation

Treatments

Outcomes



Other TTMs not included

A TRIAL OF GOAL-ORIENTED HEMODYNAMIC THERAPY IN CRITICALLY ILL PATIENTS

LUCIANO GATTINONI, M.D., LUCA BRAZZI, M.D., PAOLO PELOSI, M.D., ROBERTO LATINI, M.D.,
GIANNI TOGNONI, M.D., ANTONIO PESENTI, M.D., AND ROBERTO FUMAGALLI, M.D.,
FOR THE SvO₂ COLLABORATIVE GROUP*

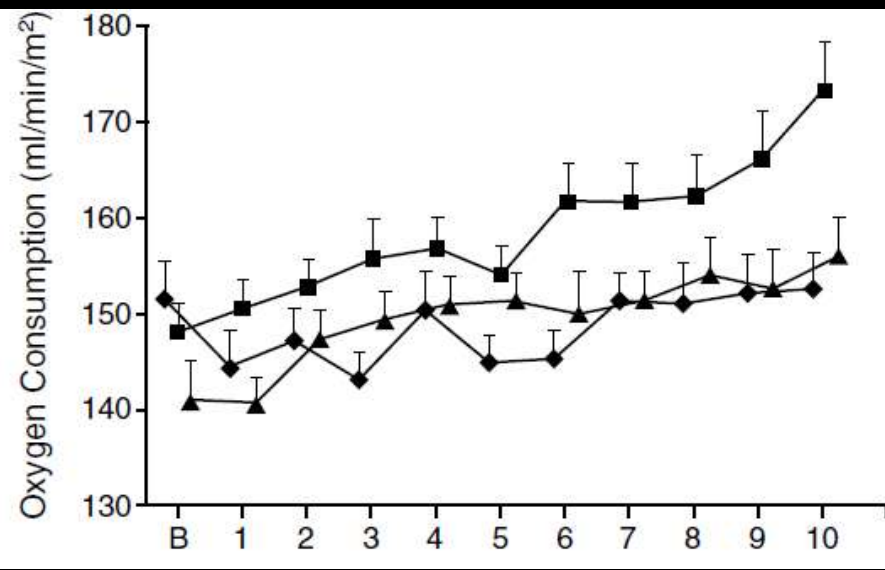
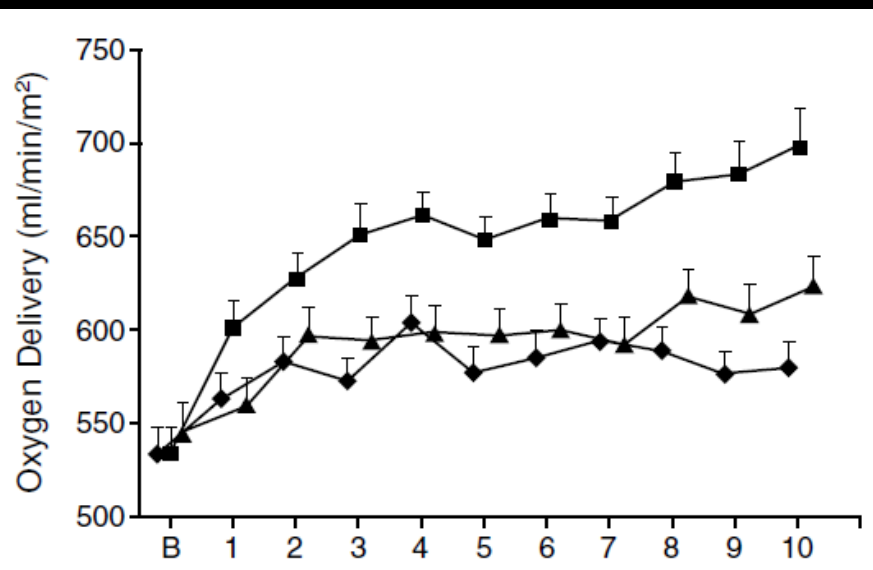
Cardiac Index Group:

CI > 4.5 L/min·m²

SvO₂ Group:

SvO₂ > 70%

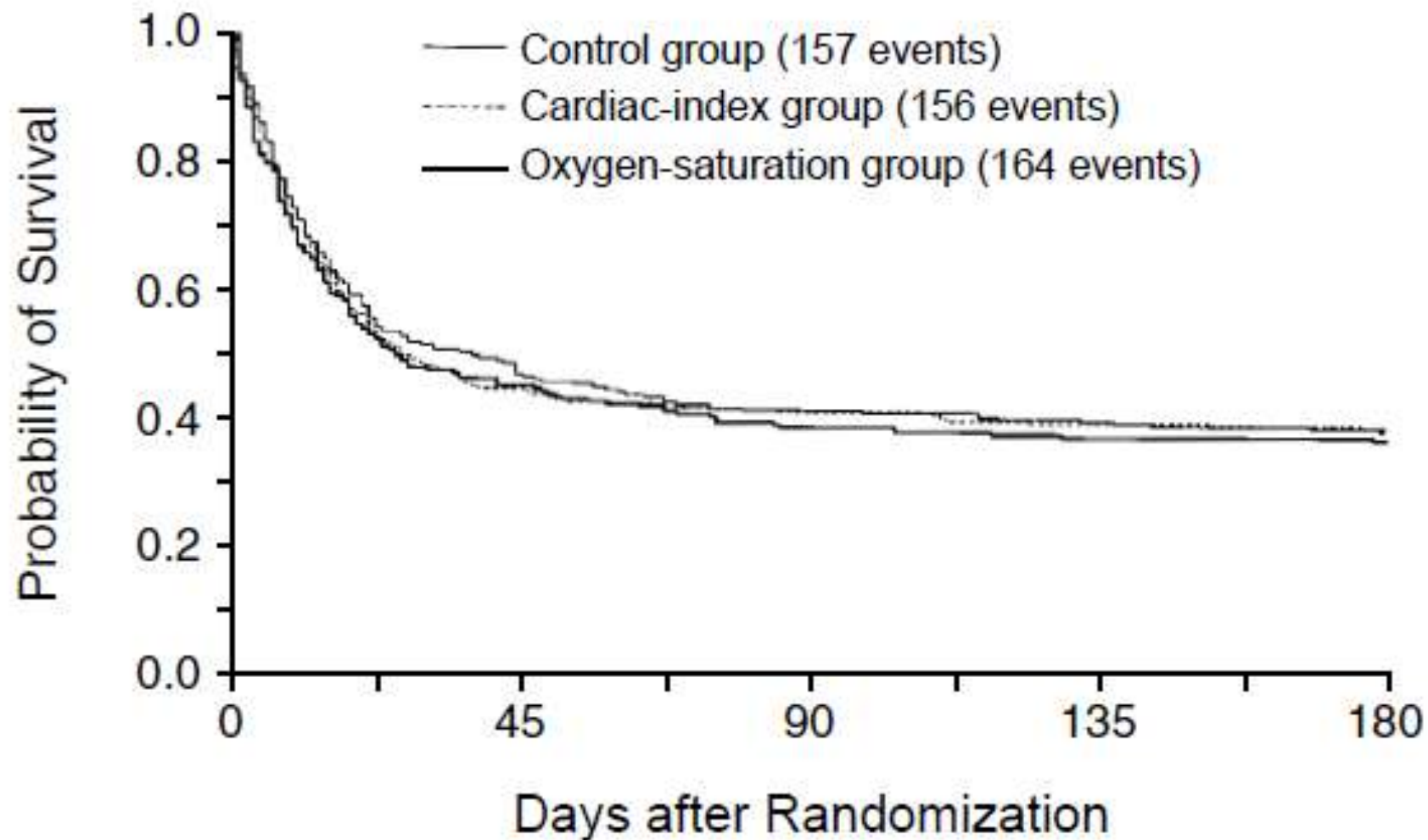
RCT, 250 patients/group
Critically ill patients



◆ Control group
■ Cardiac-index group
▲ Oxygen-saturation group

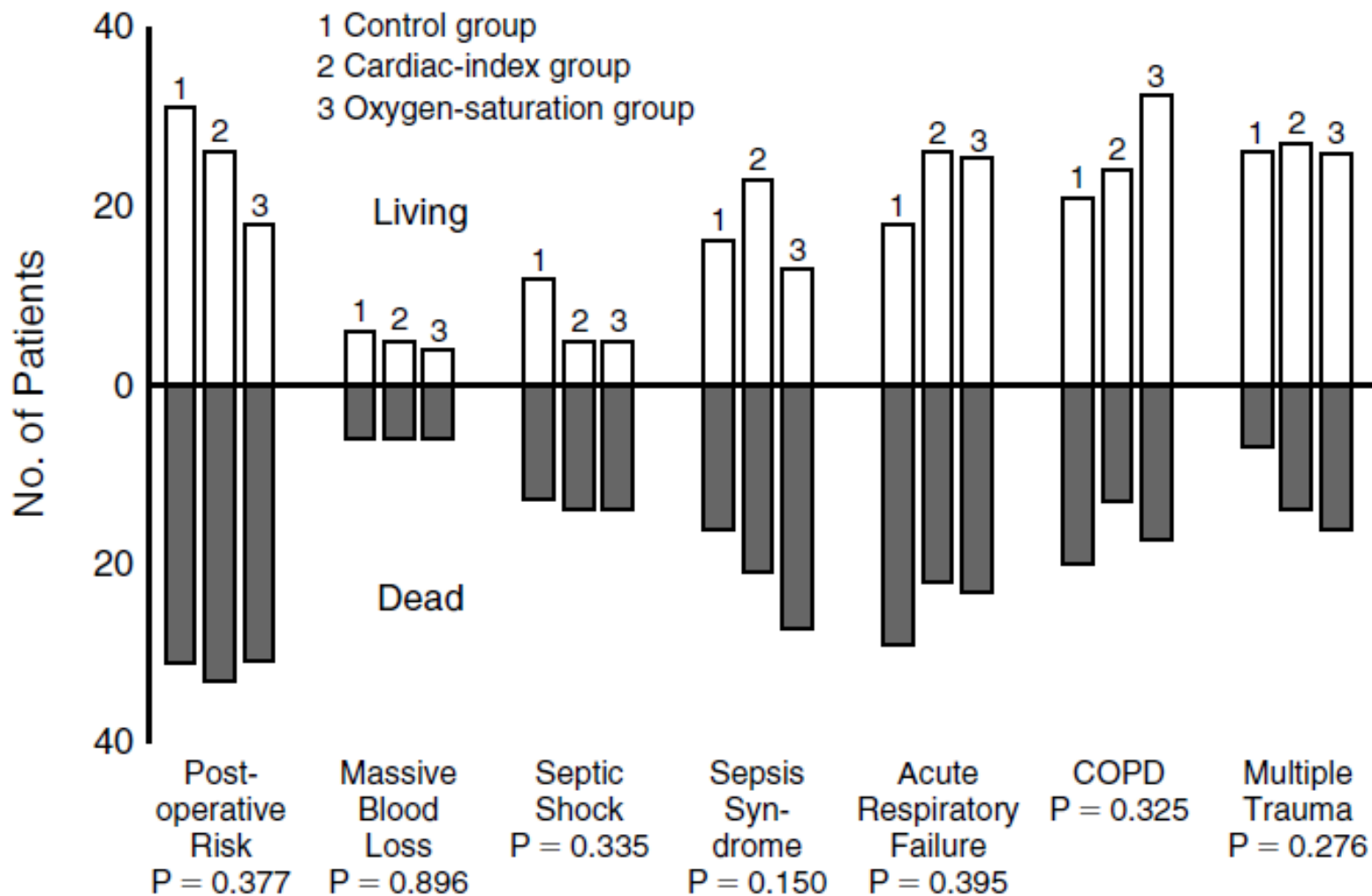
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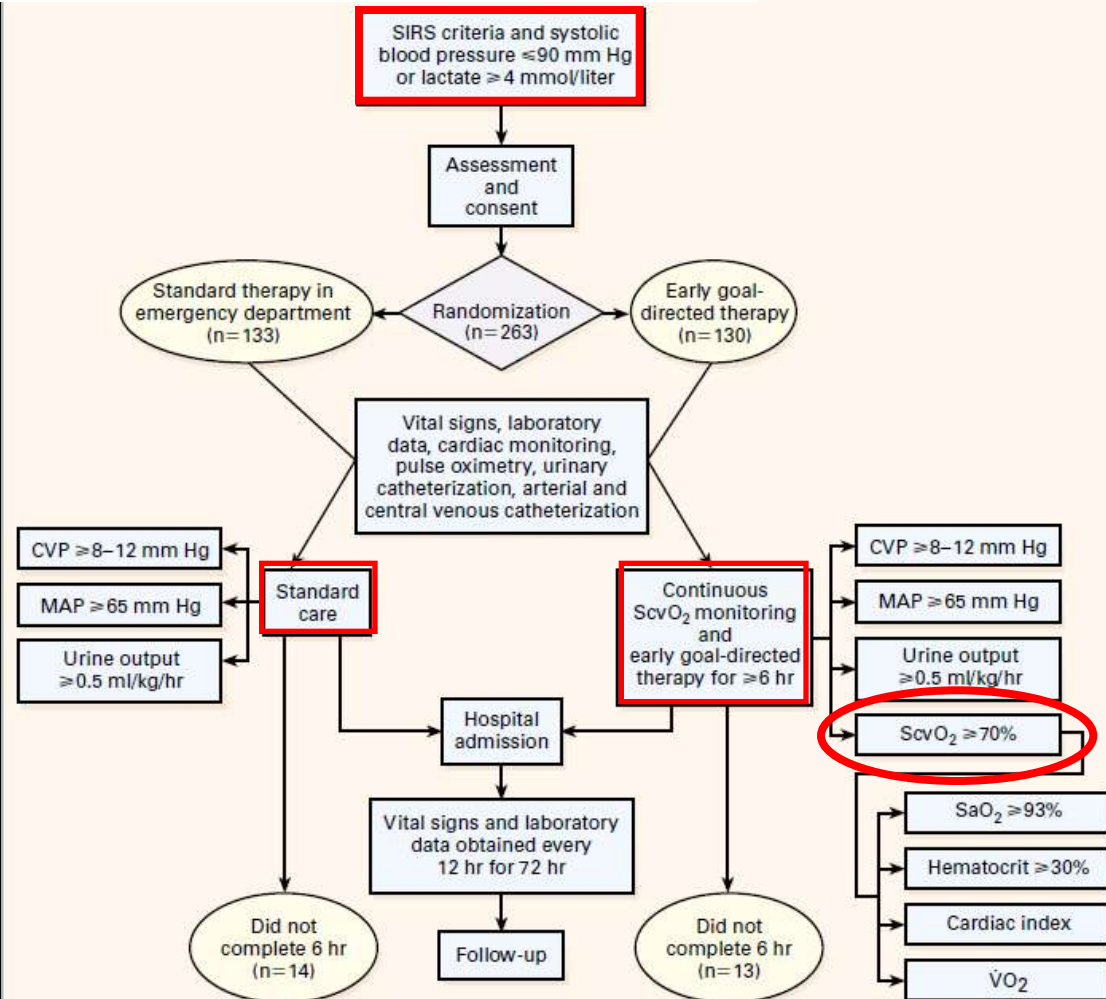


EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

n= 263; 1 ED

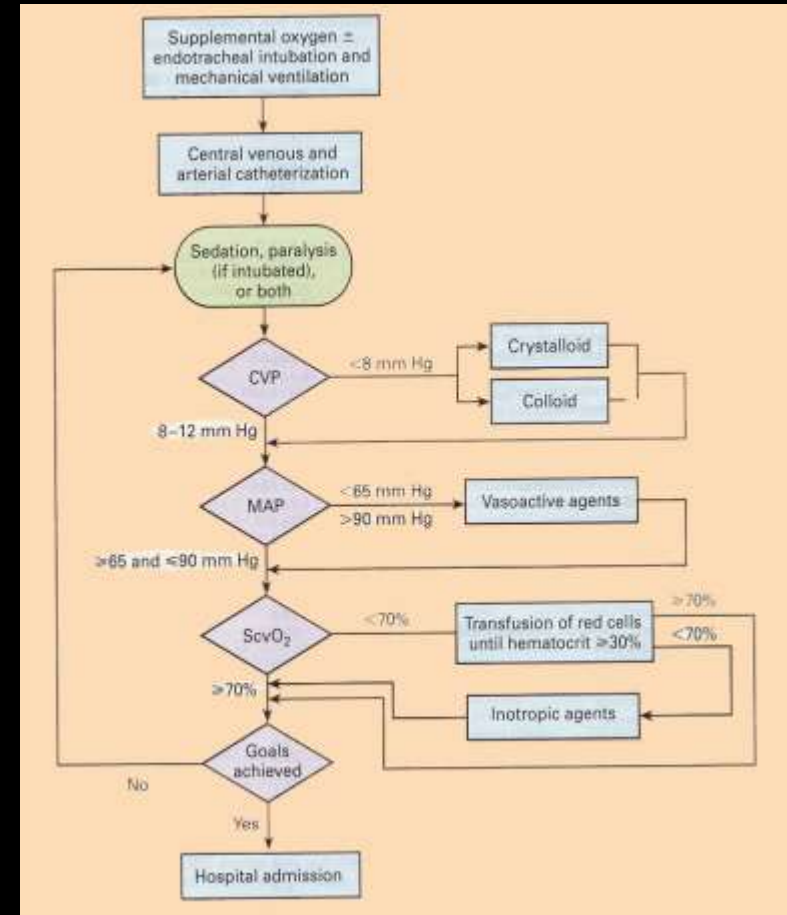
- First 6 hours
- Control: Usual care ED + ICU
- TTM:
 - Protocol in the ED, later transfer to ICU.
 - Continuous ScvO₂
 - ScvO₂ goal



Early goal directed therapy

EGDT involves:

- Identification of high risk patients.
- Monitoring: central venous catheter with continuous oxymetry.
- 6h of protocolized resuscitation with fluids and vasopressors.
- Additional protocol for \uparrow ScvO₂: inotropes and PRBC.



EGDT: Treatments

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

PROTOCOL

GOAL

GOAL

EGDT: Goals

VARIABLE AND TREATMENT GROUP	BASE LINE (0 hr)	HOURS AFTER START OF THERAPY		
		6	0-6†	7-72‡
Heart rate (beats/min)				
Standard therapy	114±27	105±25	108±23	99±18
EGDT	117±31	103±19	105±19	96±18
P value	0.45	0.12	0.25	0.04
Central venous pressure (mm Hg)				
Standard therapy	6.1±7.7	11.8±6.8	10.5±6.8	11.6±6.1
EGDT	5.3±9.3	13.8±4.4	11.7±5.1	11.9±5.6
P value	0.57	0.007	0.22	0.68
Mean arterial pressure (mm Hg)				
Standard therapy	76±24	81±18	81±16	80±15
EGDT	74±27	95±19	88±16	87±15
P value	0.60	<0.001	<0.001	<0.001
Central venous oxygen saturation (%)				
Standard therapy	49.2±13.3	66.0±15.5	65.4±14.2	65.3±11.4
EGDT	48.6±11.2	77.3±10.0	71.6±10.2	70.4±10.7
P value	0.49	<0.001	<0.001	<0.001
Lactate (mmol/liter)				
Standard therapy	6.9±4.5	4.9±4.7	5.9±4.2	3.9±4.4
EGDT	7.7±4.7	4.3±4.2	5.5±4.2	3.0±4.4
P value	0.17	0.01	0.62	0.02
Base deficit (mmol/liter)				
Standard therapy	8.9±7.5	8.0±6.4	8.6±6.0	5.1±6.7
EGDT	8.9±8.1	4.7±5.8	6.7±5.6	2.0±6.6
P value	0.81	<0.001	0.006	<0.001
Arterial pH				
Standard therapy	7.32±0.19	7.31±0.15	7.31±0.12	7.36±0.12
EGDT	7.31±0.17	7.35±0.11	7.33±0.13	7.40±0.12
P value	0.40	<0.001	0.26	<0.001

PROTOCOL

GOAL

BOTH

Early goal-directed therapy

EGDT in patients with septic shock or lactate > 4

	T	C	RRR	NNT	<i>p</i>
Hospital mortality	31%	47%	34%	6	0.009
60d mortality	44%	57%	22%	8	0.03

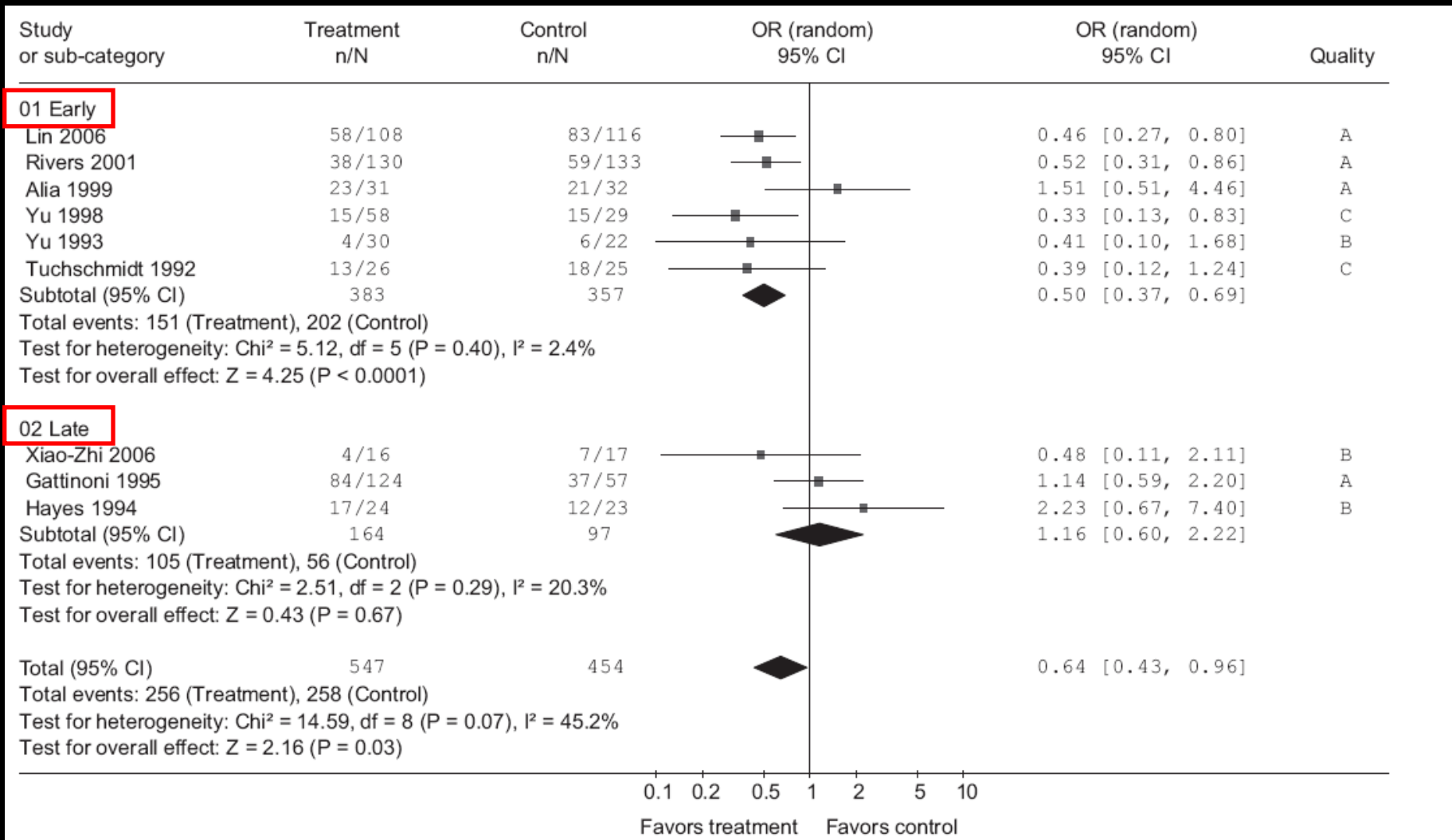
EGDT in patients with lactate >4 and no hypotension
(cryptic shock)

	T	C	RRR	NNT	<i>p</i>
Hospital mortality	20%	60,9%	67%	2.5	0.004

Quantitative Resuscitation in sepsis: Meta analysis

Study	Year	N ^a	Overall Mortality (%)	Mortality Timing	Study Location	Patient Selection	Concealment	Jadad Score	Intervention Timing	Quantitative Resuscitation Group End points ^b
Early										
Lin	2006	224	61	Hospital	ICU	A	A	2	Early	CVP, MAP, UO
Rivers	2001	263	37	Hospital	ED	A	A	4	Early	ScvO ₂
Alia	1999	63	70	ICU	ICU	A	A	1	Early	DO ₂ I
Yu	1998	87	34	ICU	ICU	A	C	1	Early	DO ₂
Yu	1993	52	19	30 day	ICU	A	B	1	Early	DO ₂
Tuchschmidt	1992	51	61	14 day	ICU	A	C	2	Early	CI
Late										
Xiao-Zhi	2006	33	33	14 day	ICU	A	B	0	Unknown	CVP, ScvO ₂
Gattinoni	1995	181	67	ICU	ICU	A	A	3	Late	CI, SVO ₂
Hayes	1994	47	62	Hospital	ICU	A	B	2	Unknown	CI, DO ₂ , VO ₂

Quantitative Resuscitation in sepsis: Meta analysis



Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

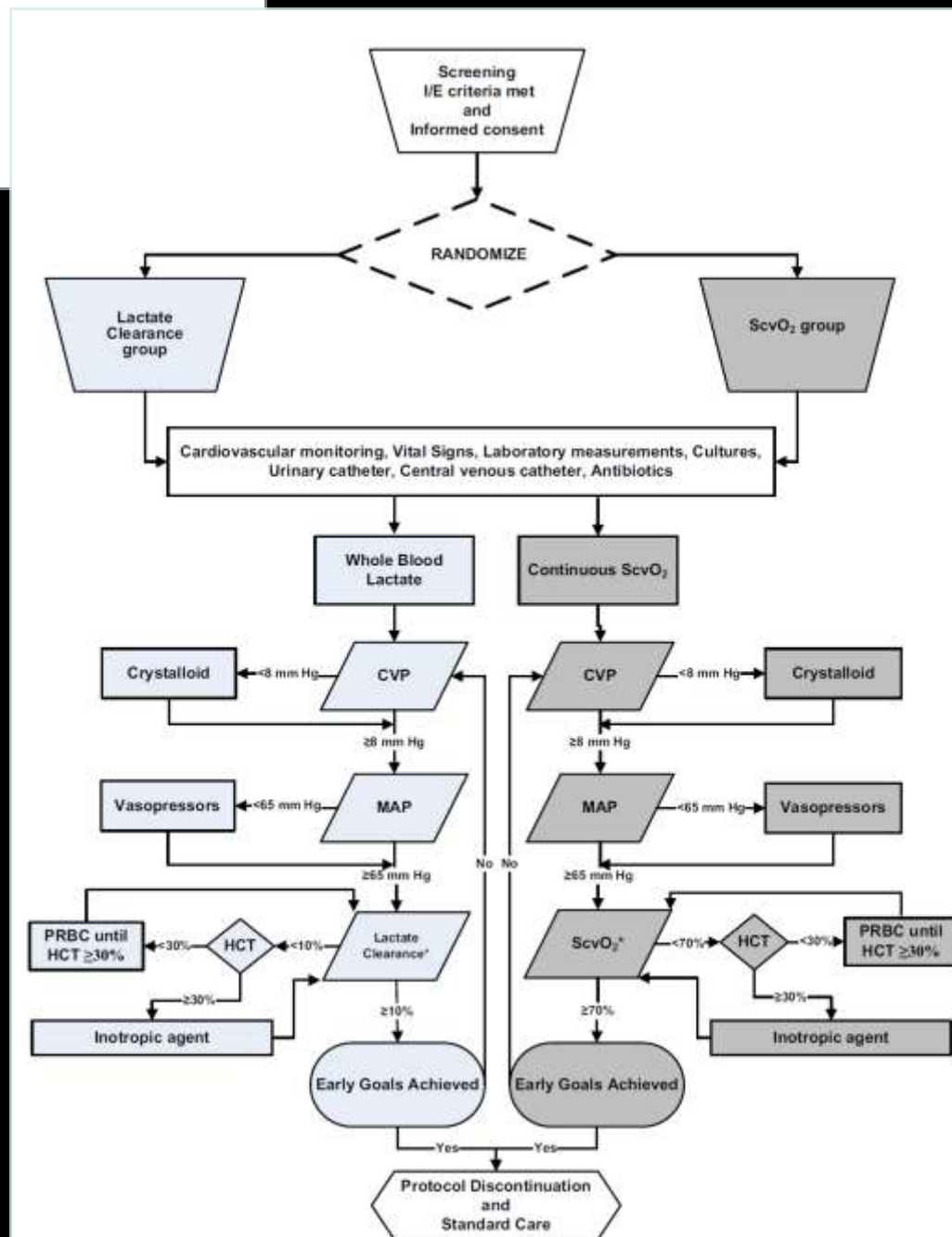
A Randomized Clinical Trial

n= 300; 3 ED
Early Septic Shock

Different Goals.

In both arms:

- All patients treated in ED.
- ICU was blinded.
- Same catheter inserted.
- Same protocol.
- Same treatments:
 - Fluids
 - Vasopressors
 - Inotropes
 - PRBC



Intervention, h	No. (%) of Patients		P Value ^a
	Lactate Clearance Group (n = 150)	ScvO ₂ Group (n = 150)	
Crystalloid volume, mean (SD), L			
0-<6	4.5 (2.36)	4.3 (2.21)	.55
6-72	12.4 (6.15)	11.8 (6.41)	.44
Vasopressor administration			
0-<6	108 (72)	113 (75)	.60
6-72	100 (67)	108 (72)	.45
Dobutamine administration			
0-<6	5 (3)	8 (5)	.57
6-72	10 (7)	13 (9)	.66
PRBC transfusion			
0-<6	11 (7)	5 (3)	.20
6-72	35 (23)	31 (21)	.78
Mechanical ventilation			
0-<6	40 (27)	39 (26)	.99
6-72	69 (46)	75 (50)	.56
Activated protein C			
0-<6	0	0	
6-72	3 (2)	2 (1)	.68
Parenteral corticosteroids			
0-<6	18 (12)	26 (17)	.25
6-72	59 (39)	51 (34)	.40

Variable	Lactate Clearance Group (n = 150)	Scvo ₂ Group (n = 150)	Proportion Difference (95% Confidence Interval)	P Value ^b
In-hospital mortality, No. (%) ^a				
Intent to treat	25 (17)	34 (23)	6 (-3 to 15)	
Per protocol	25 (17)	33 (22)	5 (-3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

- 1) Measure lactate level
- 2) Obtain blood cultures prior to administration of antibiotics
- 3) Administer broad spectrum antibiotics
- 4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
- 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
 - Measure central venous pressure (CVP)*
 - Measure central venous oxygen saturation (Scvo₂)*
- 7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, Scvo₂ of $\geq 70\%$, and normalization of lactate.

Limitations of the Rivers study

- Concerns about the use of dobutamine.
- Concerns about administering PRBC to keep hgb > 10 mg/dL.
- Uncertainty about the external validity of the EGDT trial.
- Uncertainty about the internal validity of the EGDT trial.
- Lack of uptake of EGDT

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

NEJM 2014

First 6H

RCT, 450 patients/group
Early Septic Shock

Protocol Based EGDT:

Requires Continuous Central Venous Monitoring

Indications to \uparrow DO_2 if $\text{ScvO}_2 < 70\%$

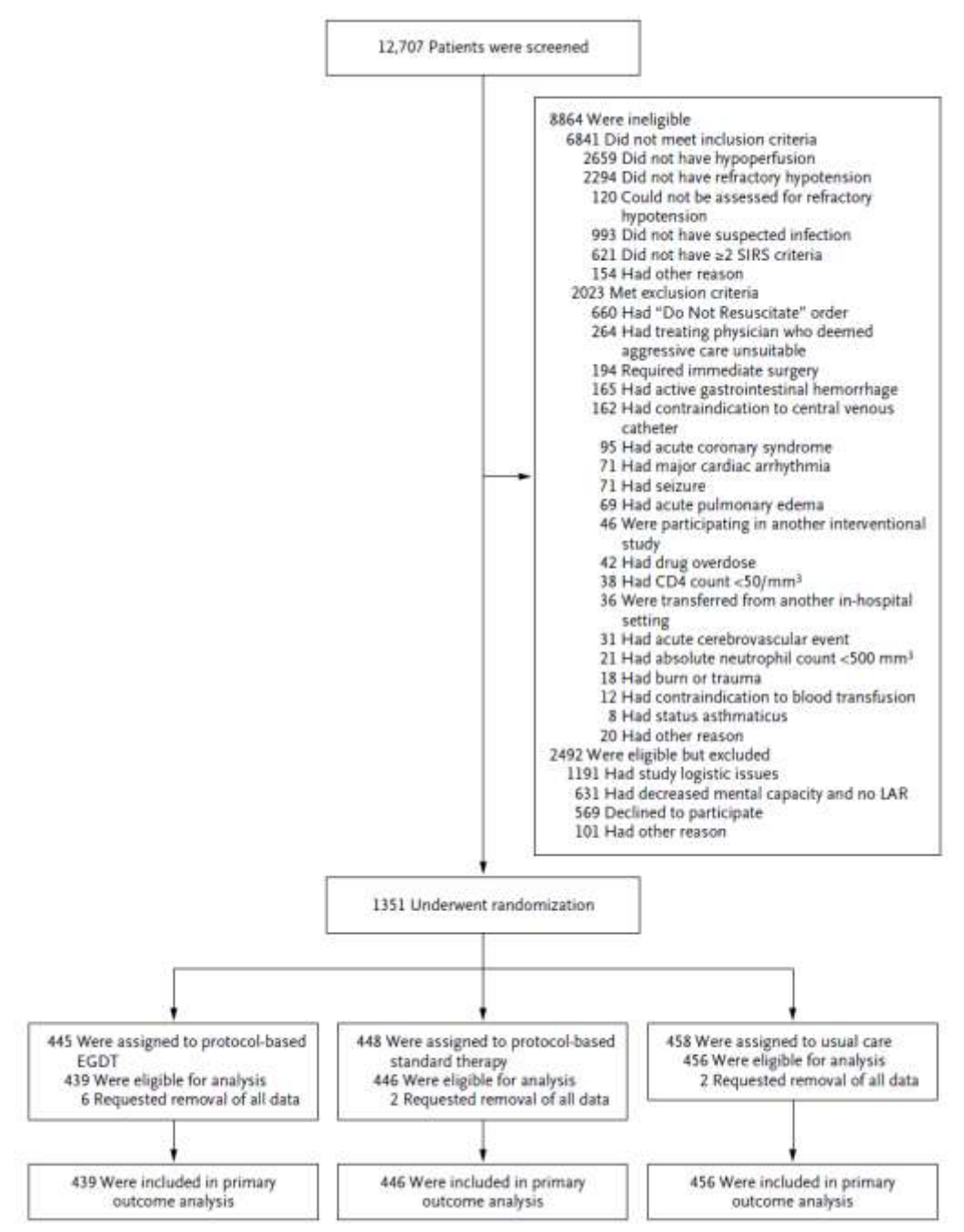
Protocol similar to Rivers

Protocol Based Standard Therapy:

Protocolized resuscitation without CV monitoring

No special indications to \uparrow DO_2

Usual care



ProCESS - EGDT

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Insert central line with oximetric port

Sedation, analgesia, +/- paralysis (if intubated)

500 cc fluid bolus if CVP < 8 mmHg

CVP

< 8 mmHg

8-12 mmHg

MAP

< 65 mm Hg

> 90 mm Hg

Vasoactive agents

≥ 65 mm Hg and ≤ 90 mmHg

ScvO₂

< 70%

If HCT < 30%, transfuse PRBCs

< 70%

Inotropic agents

≥ 70%

Goals achieved?

No

Yes

Observe

ProCESS - PSC

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

> 2 large bore (18 g or larger) IV's (Central line if unable to achieve)¹

Sedation, analgesia, +/- paralysis (if intubated)

500-1000 ml fluid bolus* (min. initial total fluid² = 2 L*, unless fluid replete/overload³)

SBP*

Shock Index (SI)

SBP ≥ 100 mmHg⁴

SBP < 100 mmHg⁴, or SI ≥ 0.8, or on vasopressors

Fluid replete/overload³?

No

Yes

Vasopressors⁴

Isotonic IVF @ 250-500 ml/hour³

If Hgb < 7.5, transfuse PRBC

Hypoperfusion^{5,6,7}?

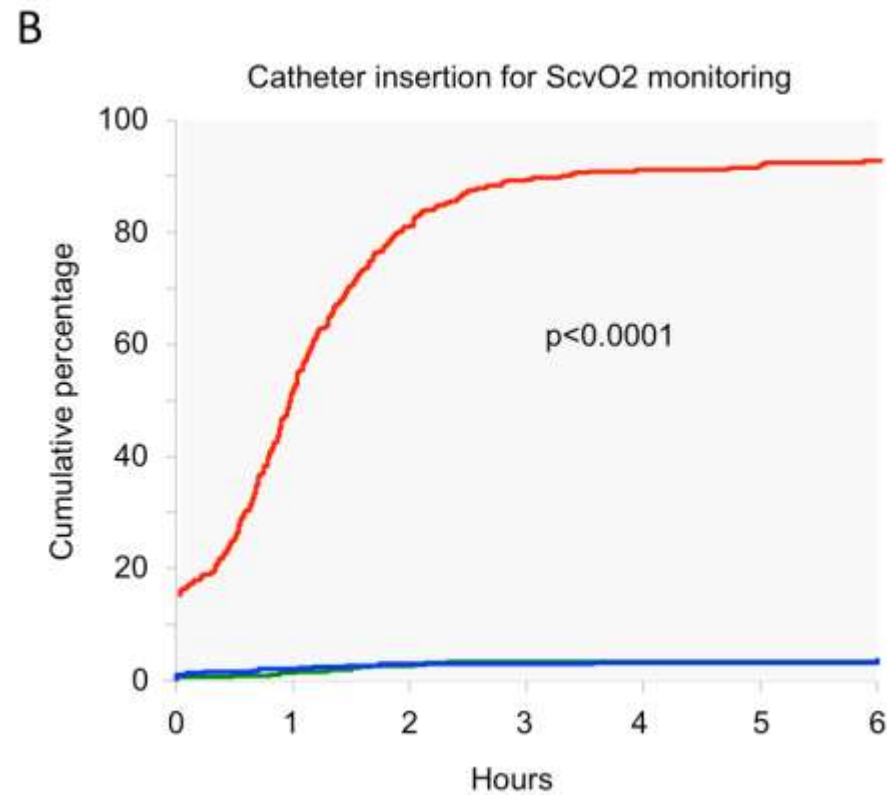
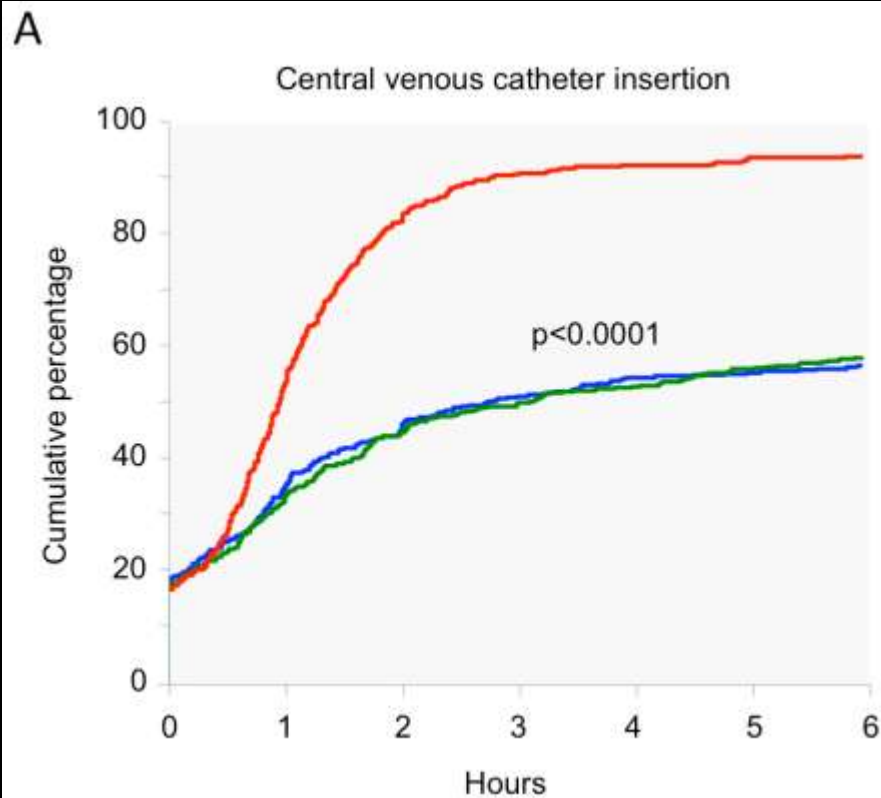
Yes

No

Lactate > 4, oliguria, mottled skin

> Reassess Q30 min
> Monitor for fluid overload³
> Consider recheck lactate, HCT

Monitorization



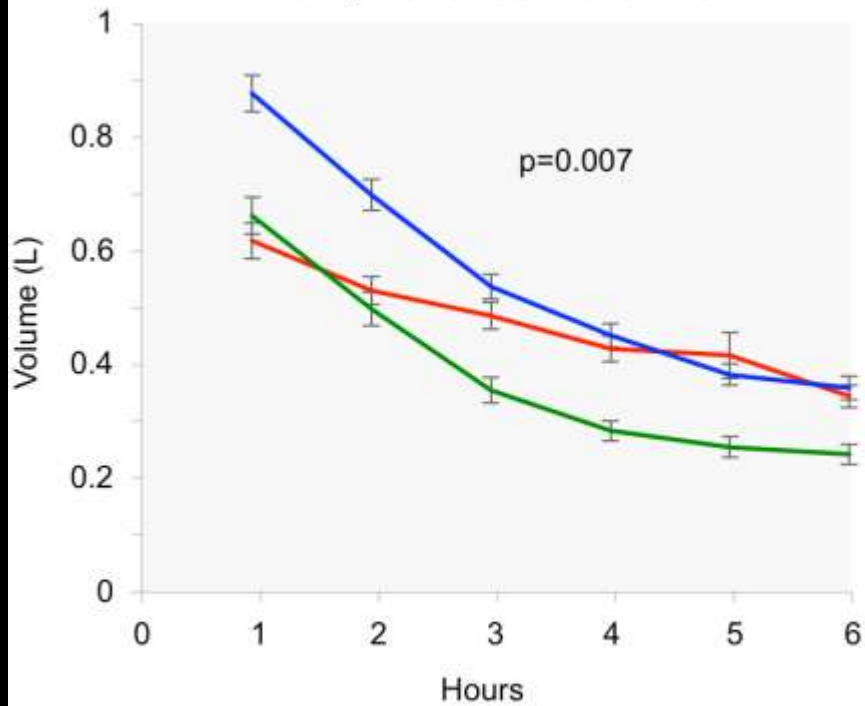
Protocol-based EGDT

Protocol-based Standard Therapy

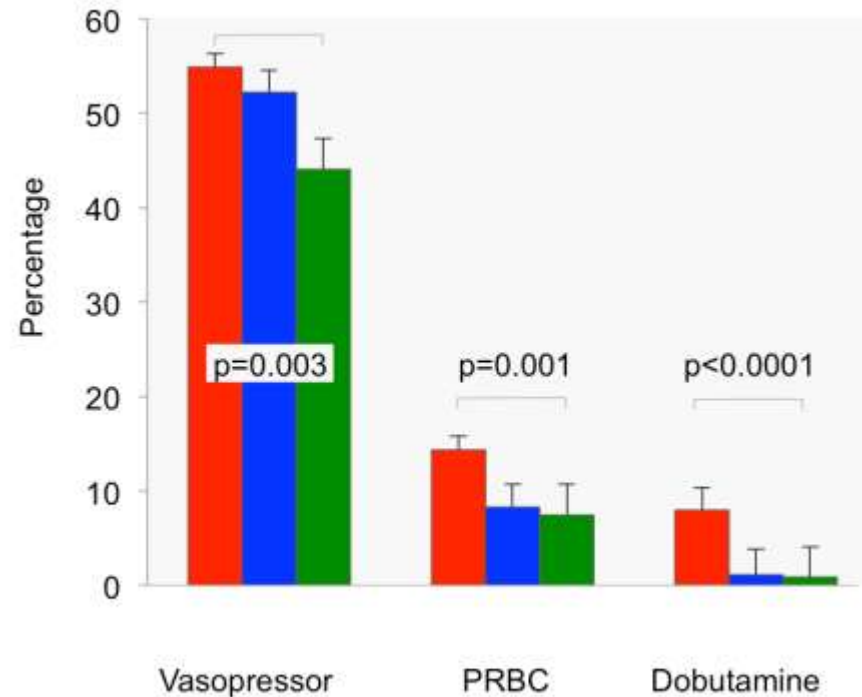
Usual care

Treatments

Hourly intravenous fluid volume



Vasoactive agent and transfusion use

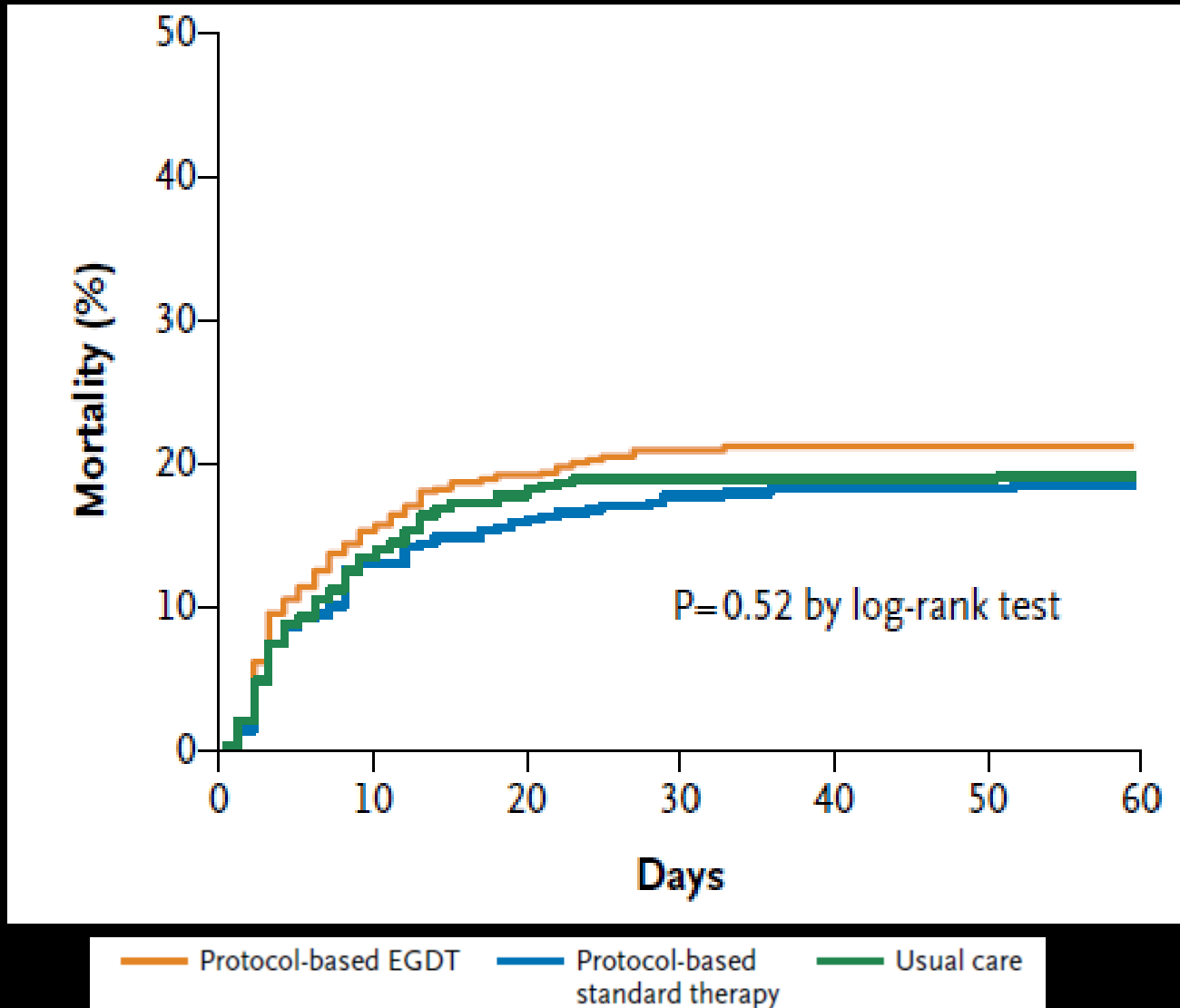


Protocol-based EGDT

Protocol-based Standard Therapy

Usual care

Outcome



Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

N Engl J Med 2014;371:1496-506.

First 6H

RCT, 800 patients/group
Early Septic Shock

Protocol Based EGDT:

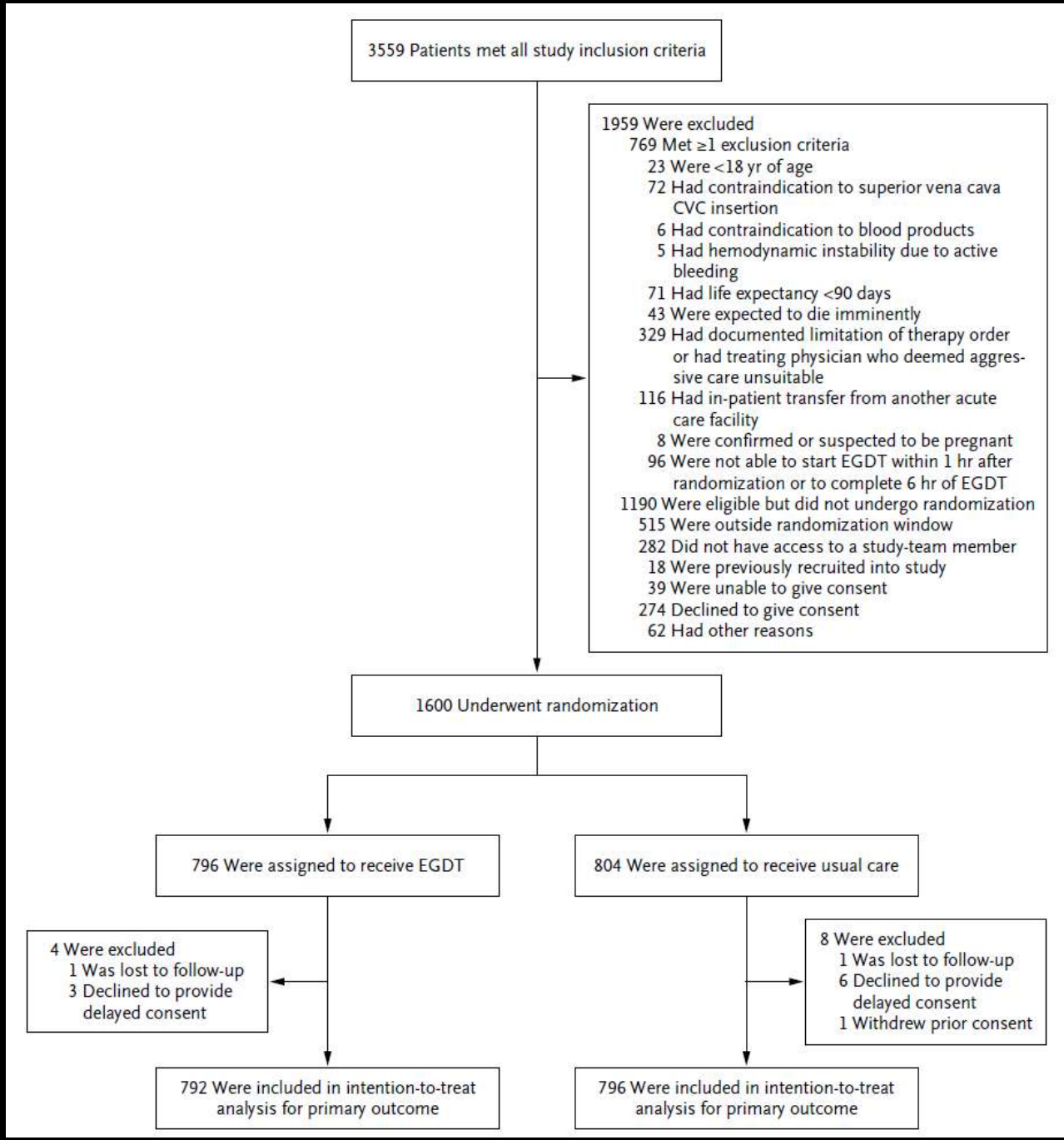
Requires Continuous Central Venous Monitoring

Indications to \uparrow DO_2 if $ScvO_2 < 70\%$

Protocol similar to Rivers

Usual care

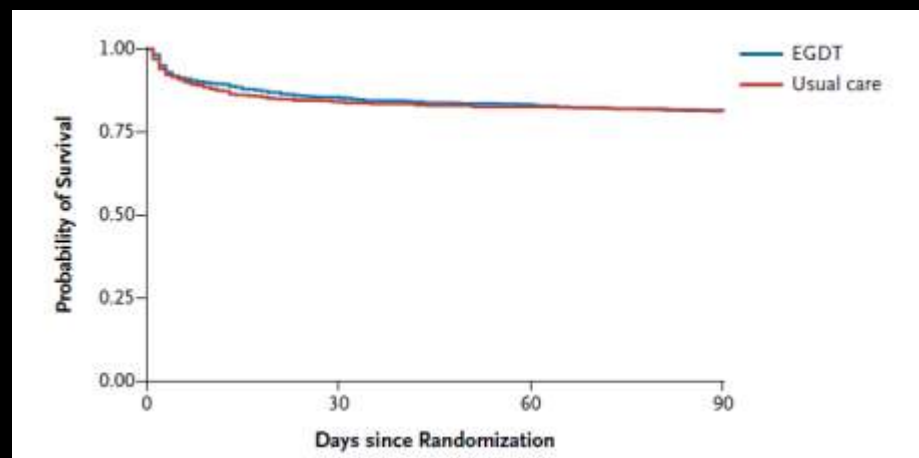
$ScvO_2$ measurement was not permitted



Intervention	0 to 6 hours		
	EGDT (N = 793)	Usual care (N = 798)	P Value
Intravenous fluids, ^c			
Total - ml	1964 ± 1415	1713 ± 1401	<0.001
Total - ml/kg	26.8 ± 20.6	23.2 ± 21.2	<0.001
Crystalloids - ml	1547 ± 1351	1374 ± 1335	0.01
Crystalloids - ml/kg	21.1 ± 19.8	18.7 ± 19.9	0.02
Colloids - ml	323 ± 672	249 ± 552	0.02
Colloids - ml/kg	4.4 ± 8.9	3.3 ± 7.5	0.01
Vasopressor infusion - no./total no. (%) ^d	528/793 (66.6)	461/798 (57.8)	<0.001
Blood products			
Red-cell transfusion - no./total no. (%)	108/793 (13.6)	56/798 (7.0)	<0.001
Dobutamine infusion - no./total no. (%)	122/793 (15.4)	21/798 (2.6)	< 0.001
Monitoring inserted - no./total no. ^e			
Arterial catheter	725/793 (91.4)	609/798 (76.3)	< 0.001
Central venous catheter	109/793 (13.7)	494/798 (61.9)	< 0.001
ScvO ₂ central venous catheter ^f	714/793 (90.0)	3/798 (0.4)	< 0.001

Table 2. Study Outcomes.

Variable	EGDT (N=793)	Usual Care (N=798)	Relative Risk (95% CI)	Risk Difference (95% CI)* <i>percentage points</i>	P Value
Primary outcome: death by day 90 — no./total no. (%)	147/792 (18.6)	150/796 (18.8)	0.98 (0.80 to 1.21)	-0.3 (-4.1 to 3.6)	0.90
Secondary outcomes					
Median duration of stay (IQR)†					
Emergency department — hr	1.4 (0.5–2.7)	2.0 (1.0–3.8)			<0.001
ICU — days	2.8 (1.4–5.1)	2.8 (1.5–5.7)			0.81
Hospital — days	8.2 (4.9–16.7)	8.5 (4.9–16.5)			0.89
Use and duration of organ support‡					
Invasive mechanical ventilation — no./total no. (%)	238/793 (30.0)	251/798 (31.5)	0.95 (0.82 to 1.11)	-1.4 (-6.0 to 3.1)	0.52
Median duration of invasive mechanical ventilation (IQR) — hr	62.2 (23.5–181.8)	65.5 (23.0–157.9)			0.28
Vasopressor support — no./total no. (%)	605/793 (76.3)	525/798 (65.8)	1.16 (1.09 to 1.24)	10.5 (6.1 to 14.9)	<0.001
Median duration of vasopressor support (IQR) — hr	29.4 (12.9–61.0)	34.2 (14.0–67.0)			0.24
Renal-replacement therapy — no./total no. (%)	106/793 (13.4)	108/798 (13.5)	0.99 (0.77 to 1.27)	-0.2 (-3.5 to 3.2)	0.94
Median duration of renal-replacement therapy (IQR) — hr§	57.8 (25.3–175.0)	85.9 (29.3–182.9)			0.40
Tertiary outcomes — no./total no. (%)					
Death by day 28	117/792 (14.8)	127/797 (15.9)	0.93 (0.73 to 1.17)	-1.2 (-4.7 to 2.4)	0.53
Death by the time of discharge from ICU	79/725 (10.9)	85/661 (12.9)	0.85 (0.64 to 1.13)	-2.0 (-5.4 to 1.5)	0.28
Death by the time of discharge from hospital¶	115/793 (14.5)	125/797 (15.7)	0.92 (0.73 to 1.17)	-1.2 (-4.7 to 2.3)	0.53



Comments

- Early recognition of hypotension or tissue hypoperfusion in all trials.
- Patients were resuscitated with at least 20 ml/kg before inclusion.
- Less severe patients than in Rivers study.
- Sepsis protocols based in SSC guidelines in most of the centers.
- Aprox 60% of patients have a central line in place in usual care.

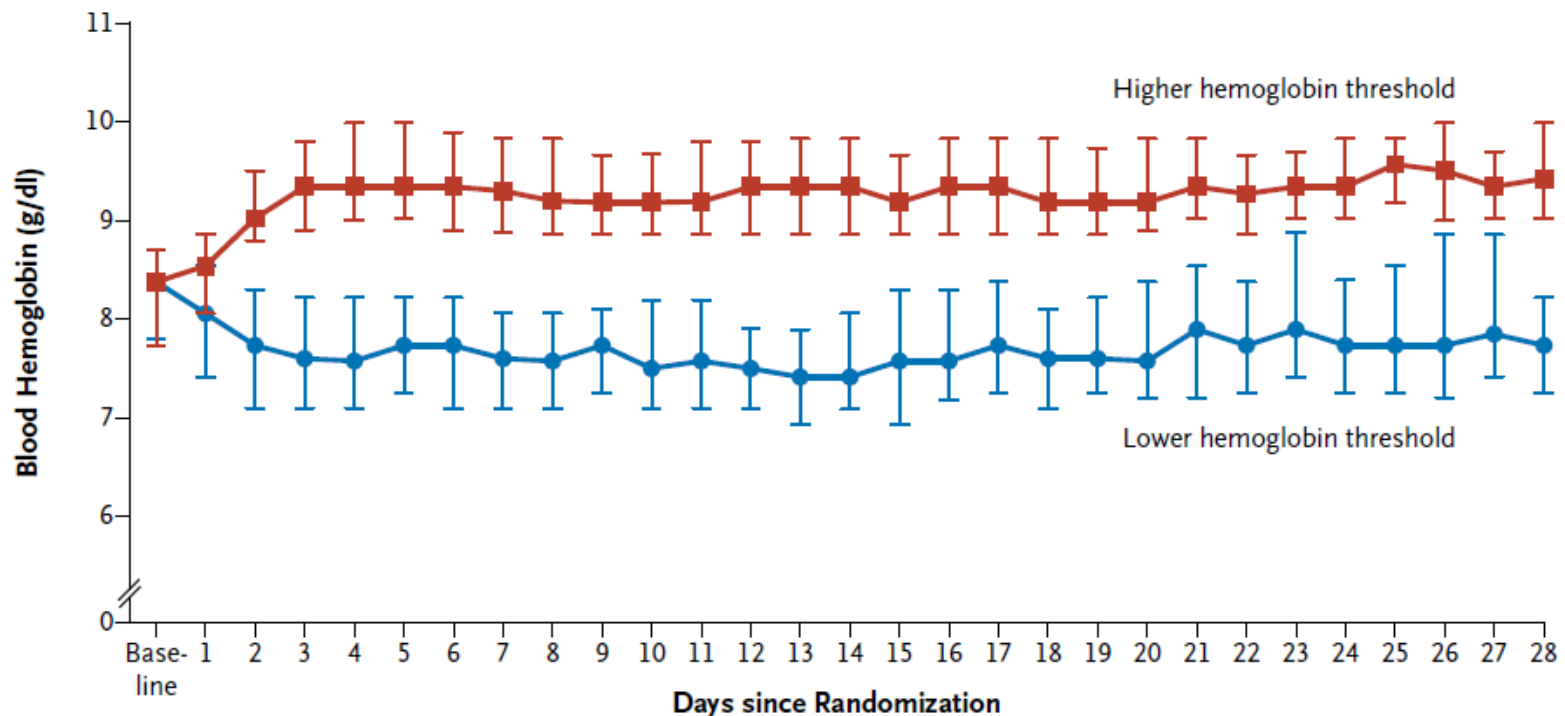
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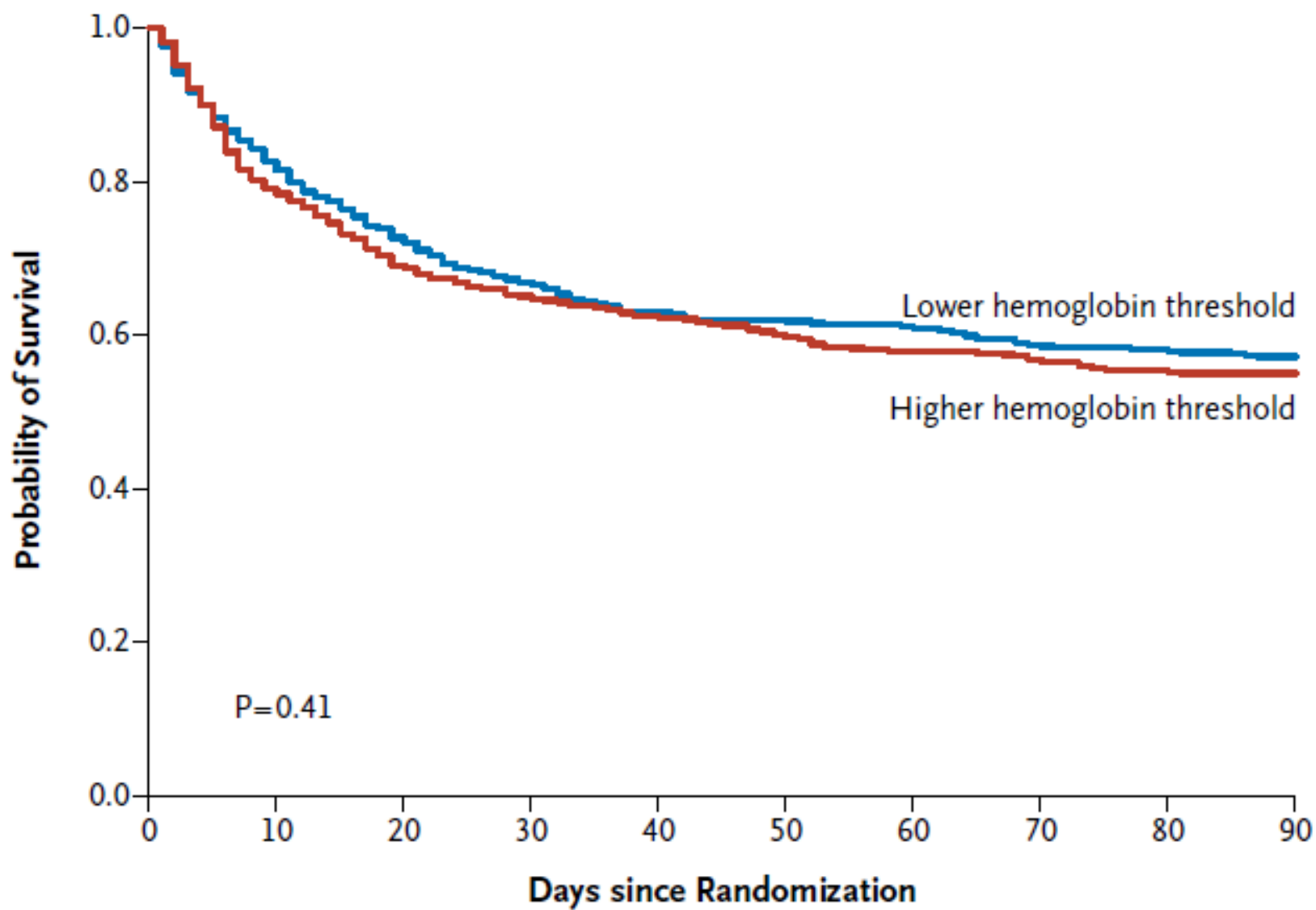
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Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock





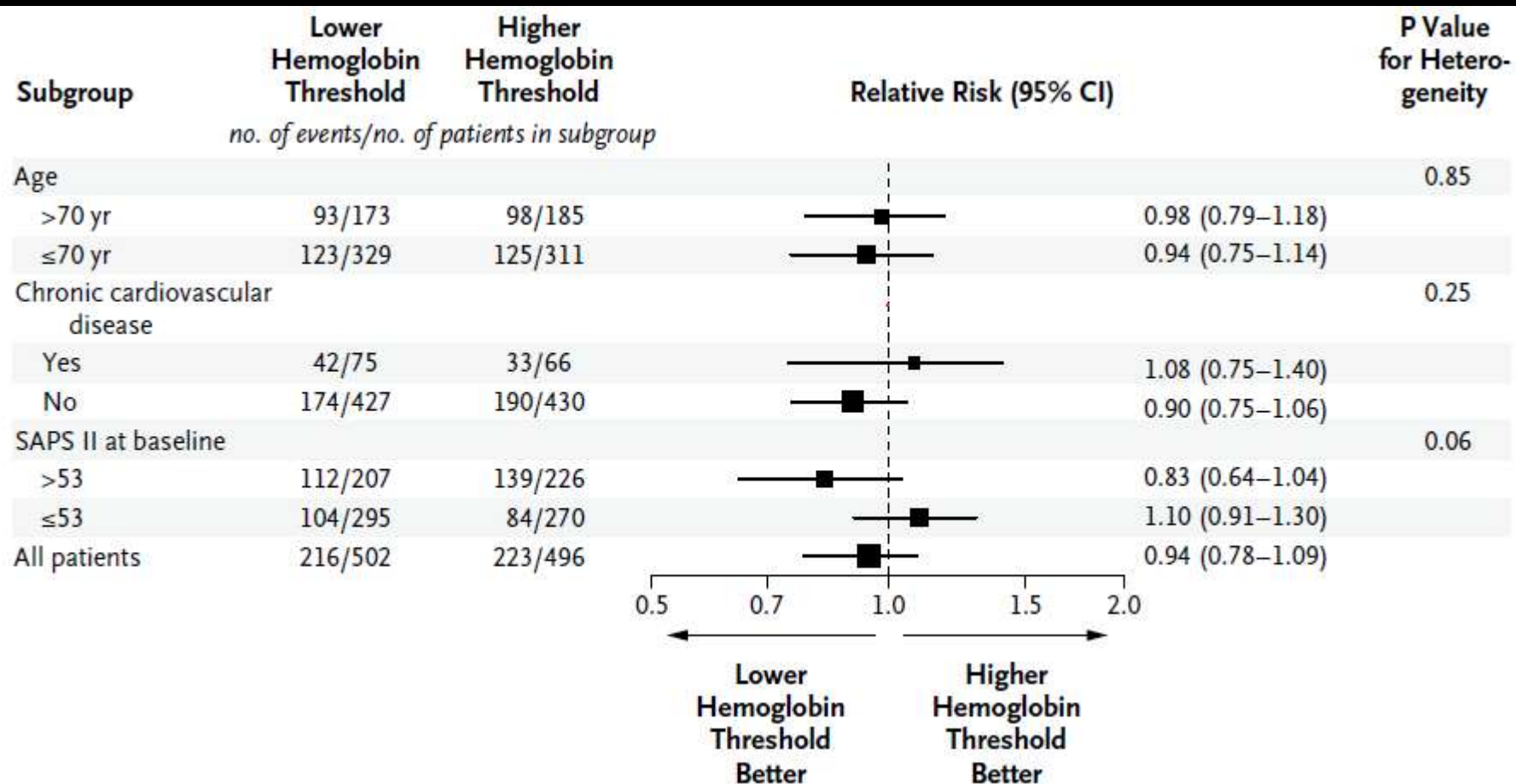


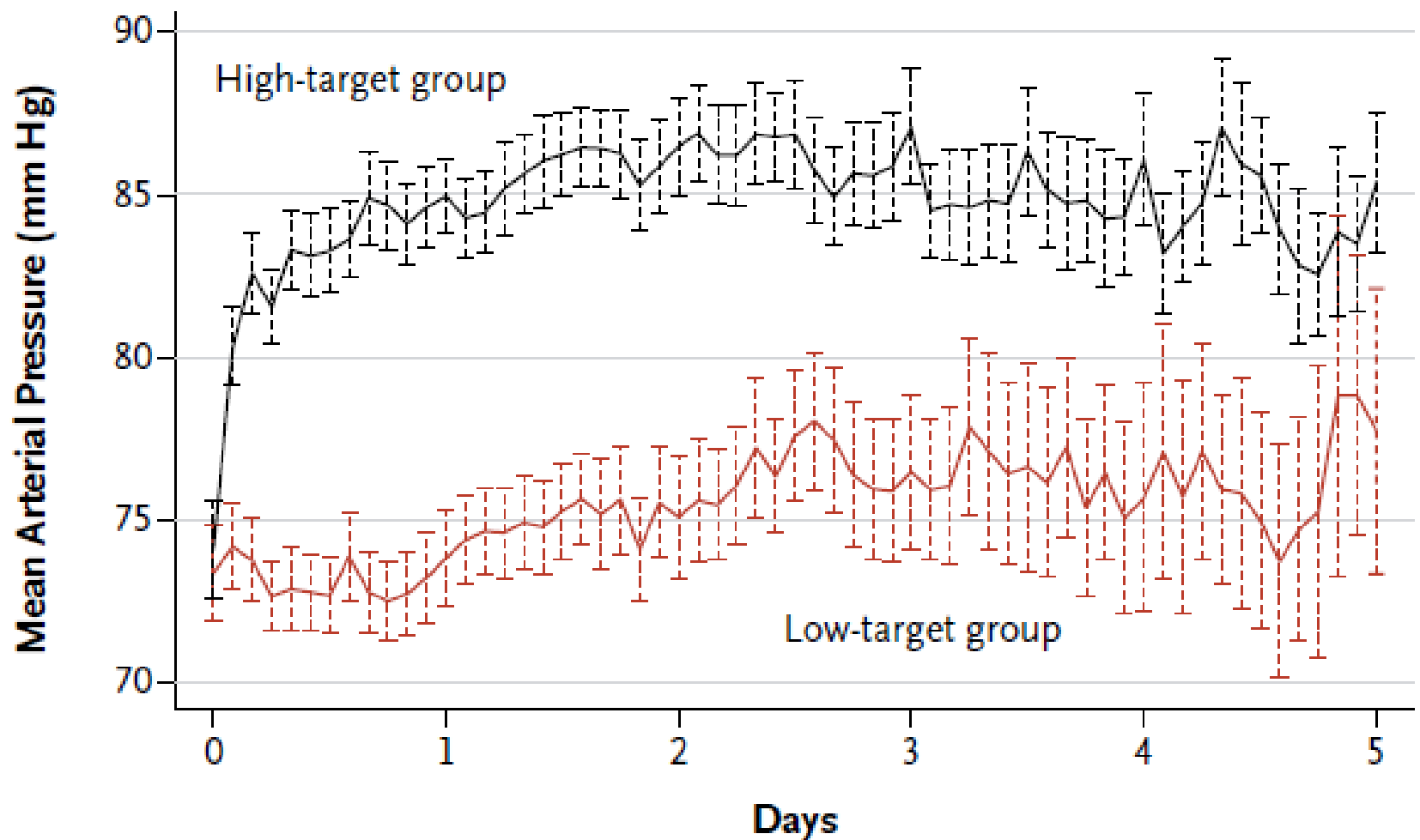
Table S14. Post-hoc analyses of number of patients with myocardial ischemia

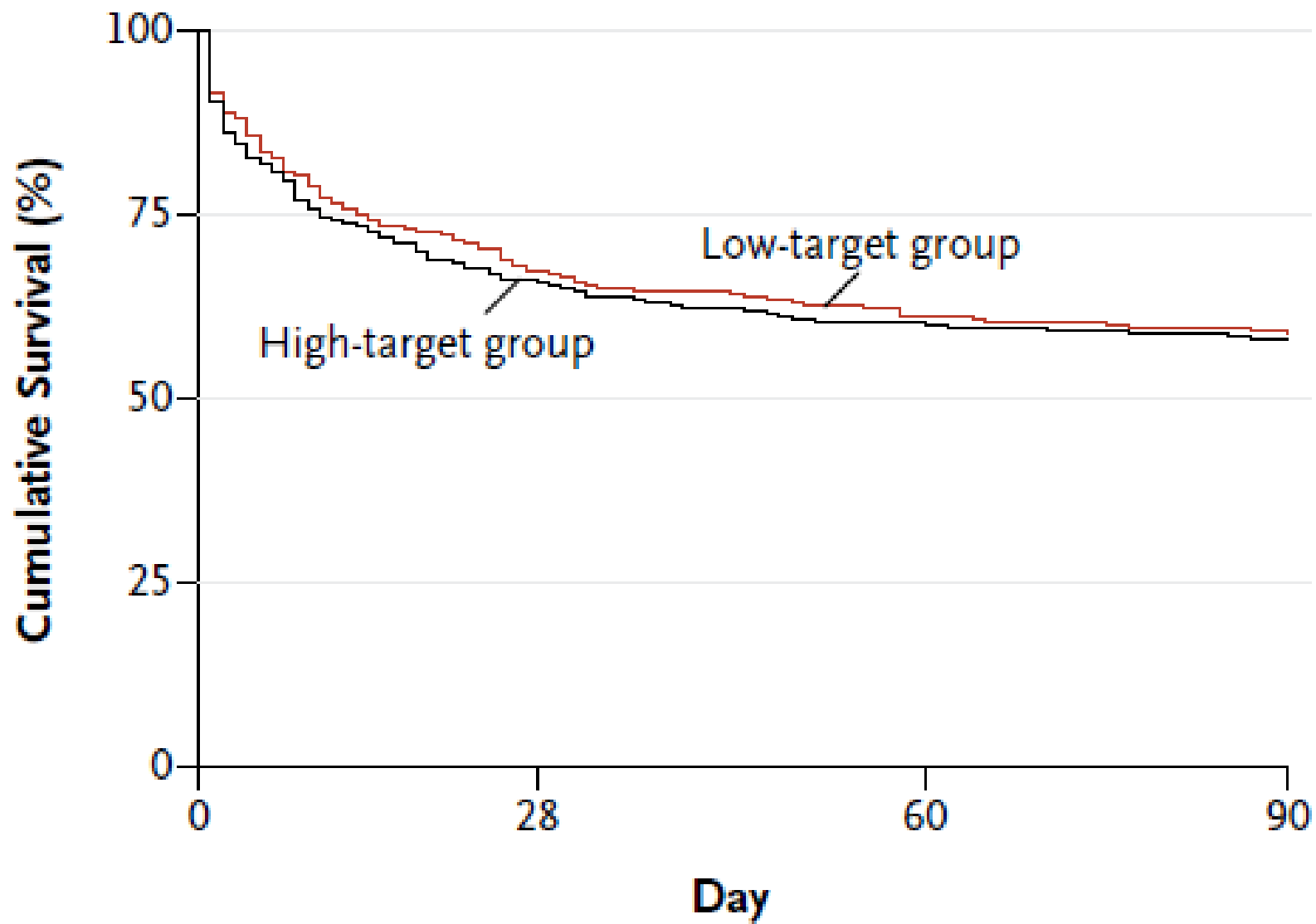
	Lower Hb-threshold	Higher Hb-threshold	Relative Risk (95% CI)	P-value*
<i>no./total no. (%)</i>				
Myocardial ischemia †	13 / 488 (2.7)	6 / 489 (1.2)	2.17 (0.83 – 5.67)	0.10
STEMI ‡	4 / 488 (0.8)	1 / 489 (0.2)	4.01 (0.45 – 35.73)	0.18
Non-STEMI/unstable angina §	9 / 488 (1.8)	5 / 489 (1.0)	1.80 (0.61 – 5.34)	0.28

High versus Low Blood-Pressure Target in Patients with Septic Shock

NEJM 2014

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D.,





Clinical trials on severe sepsis/septic shock (NEJM, 2014)

Study	ALBIOS	SEPSISPAM	TRISS	ProCESS	ARISE
Geographical area	Europe (Italy)	Europe (France)	Europe (Scandinavia)	USA	Australia/New Zealand (90%)
Patients enrolled (N)	1810	776	998	1341	1591
Death at 90 days - No./Total (%)	754/1781 (42.2%)	334/776 (43.0%)	439/998 (44.0%)	396/1232 (32.0%)	297/1588 (18.7%)
Mechanical ventilation	1446/1810 (79.8%)	594/776 (76.5%)	695/998 (69.0%)	188/1341 (14%)	243/1591 (15.2%)
Severity Score	SAPS II \approx 48	SAPS II \approx 56.1-57.2	SAPS II \approx 51-52	APACHE II \approx 20-21	APACHE II \approx 15-16
Expected Hospital Mortality	41%	60%-62%	48%-51%	38.1%-41.6%	22.9%-25.6%

Conclusions

La resucitació del pacient amb sèpsia consta de 3 fases:

Fase 1: 1H

- Reconeixement immediat de la hipotensió i la hipoperfusió refractària a fluids (aprox 20 ml/kg).
Determinació de Lactat

Fase 2: 6H

- La resucitació precoç (< 6 hores) és un dels pilars del tractament de la sèpsia.
- Cal fer-ho conjuntament amb la resta de mesures: antibiòtic i control del focus.
- Les mesures de disminució del VO₂ formen part de l'algoritme.

Conclusions

Fase 2:

- La inserció de una via central en aquesta fase és molt freqüent als estudis i pot ser necessari en molts pacients.
- La EGDT és segura però utilitza més fluids, vasoactius i transfusions sense un clar benefici. Aquest ús està induït per la utilització de la PVC i la SvO₂ per guiar la resucitació no està clara
- Administrar fluids i vasopresors per TAM \geq 65 mmHg.

Conclusions

Fase 2:

- La administració de CH en pacients amb HGB > 7 s'ha de individualitzar: hipoperfusió sostinguda, isquemia coronaria, etc.
- La administració de DBT sense monitorització avançada és qüestionable.
- Cal identificar els malalts que mantenen la hipòxia tissular: 2^o lactat, SvO₂, oligúria, livideses.

Fase 3:

- El pacient que no respon a la resucitació inicial, cal que ingressi a UCI per continuar la resucitació amb monitorització avançada.

THANK
YOU

rferrer@mutuaterrassa.es