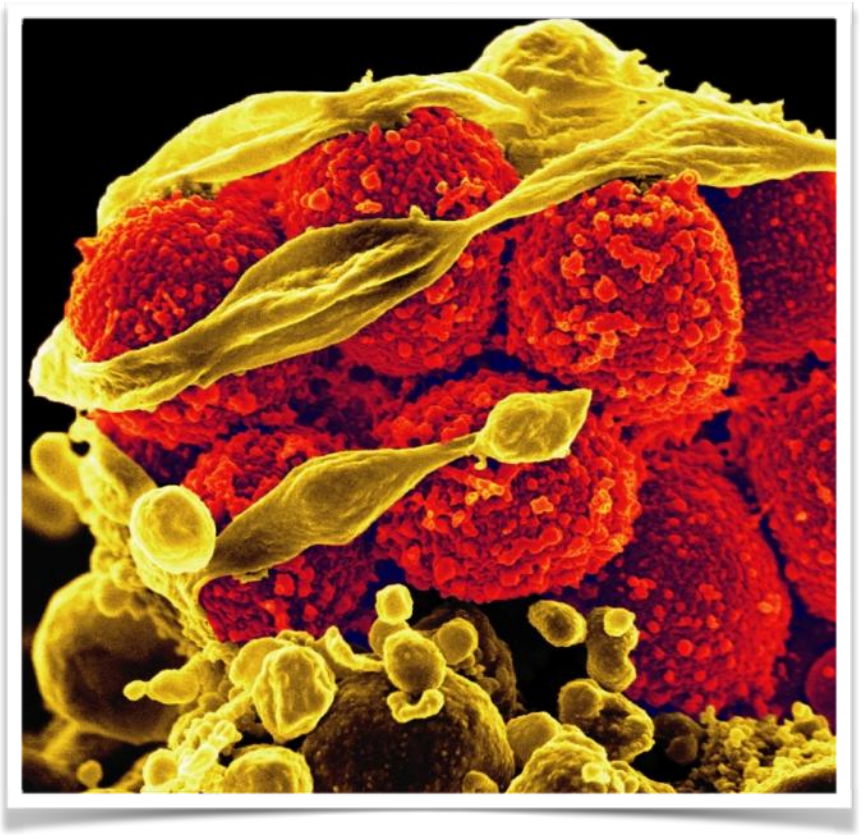

Beta-Blockers In Sepsis

Should we slow the septic heart or our own enthusiasm?

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Definitions

Definition	SIRS*	Hypotension**	End-organ damage
Sepsis	✓	+/-	+/-
Severe sepsis	✓	+/-	✓
Sepsis-induced tissue hypotension	✓	✓	
Septic shock	✓	✓ **(despite fluid resuscitation)**	✓

*SIRS = systemic inflammatory response syndrome

** = SBP <90 or MAP <70 or SBP ⬇ 40 mm Hg

Crit Care Med 2013; 41:580–637

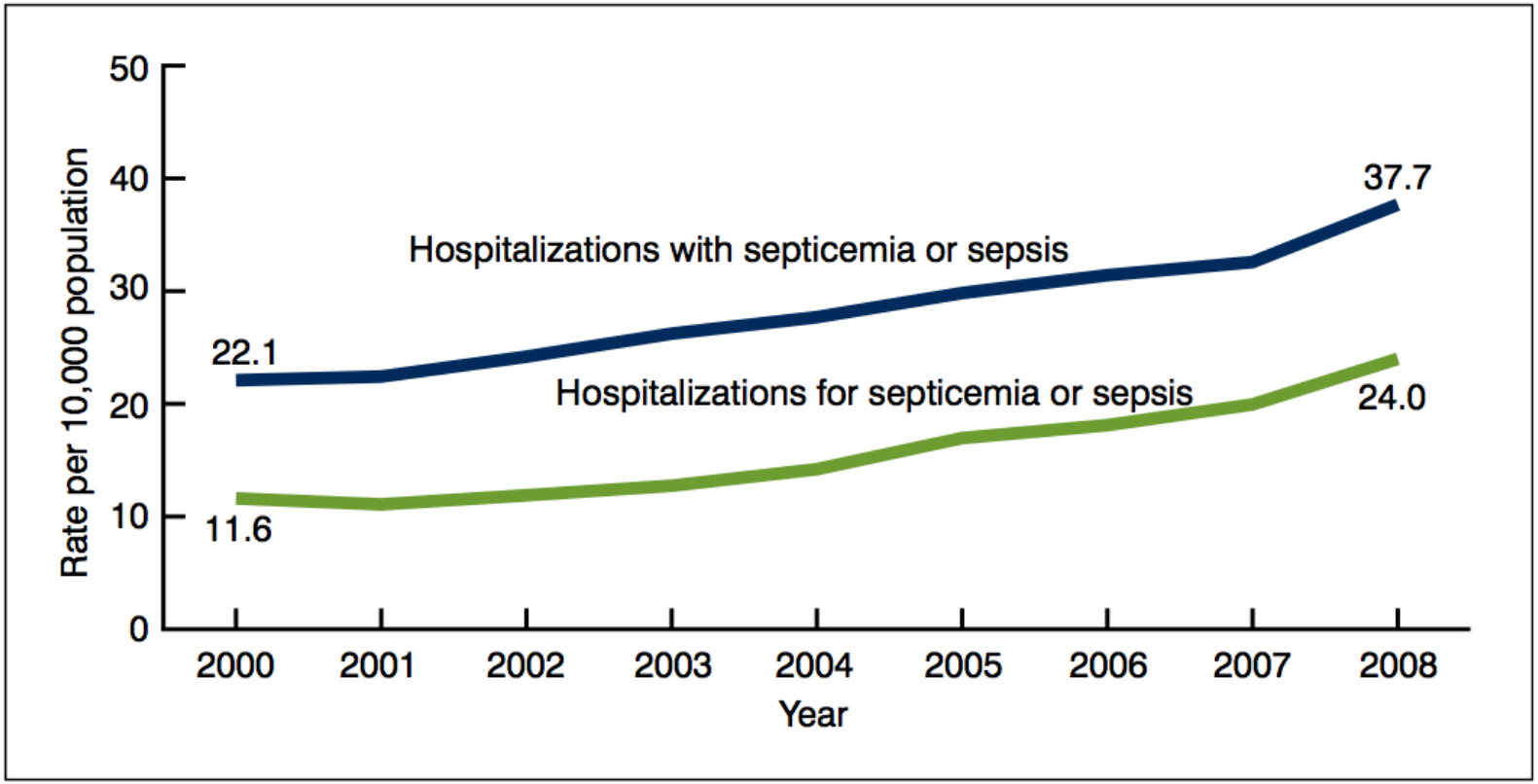
“Shock is the manifestation of the rude unhinging of the machinery of life.”

–Samuel Gross, 1862

Sepsis

Hospitalization rates for septicemia or sepsis more than doubled from 2000 through 2008.

Figure 1. Hospitalizations for and with septicemia or sepsis



CDC/NCHS, National Hospital Dischargae Survey, 2008

Sepsis

Table. Hospitalizations for septicemia or sepsis compared with hospitalizations for other diagnoses, by discharge disposition, 2008

Characteristic	Septicemia or sepsis	Other diagnoses
Disposition	**Percent**	
Routine[1]	39	79
Transfer to other short-term care facility[1]	6	3
Transfer to long-term care institution[1]	30	10
Died during the hospitalization[1]	17	2
Other or not stated	8	6
Total	100	100

[1]Difference is statistically significant at the 0.05 level.
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

Sepsis

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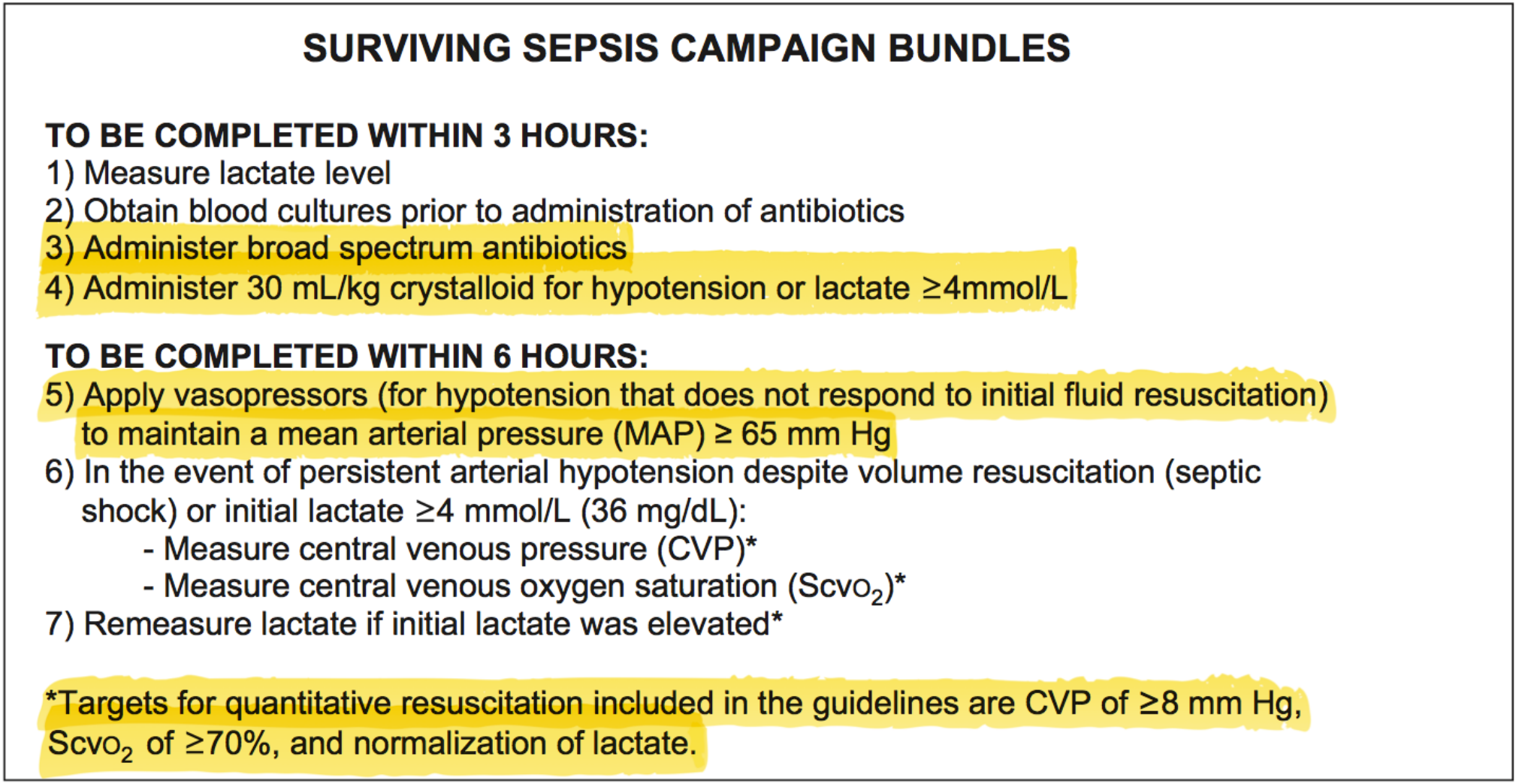
Sepsis



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 ≥4mmol/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 ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

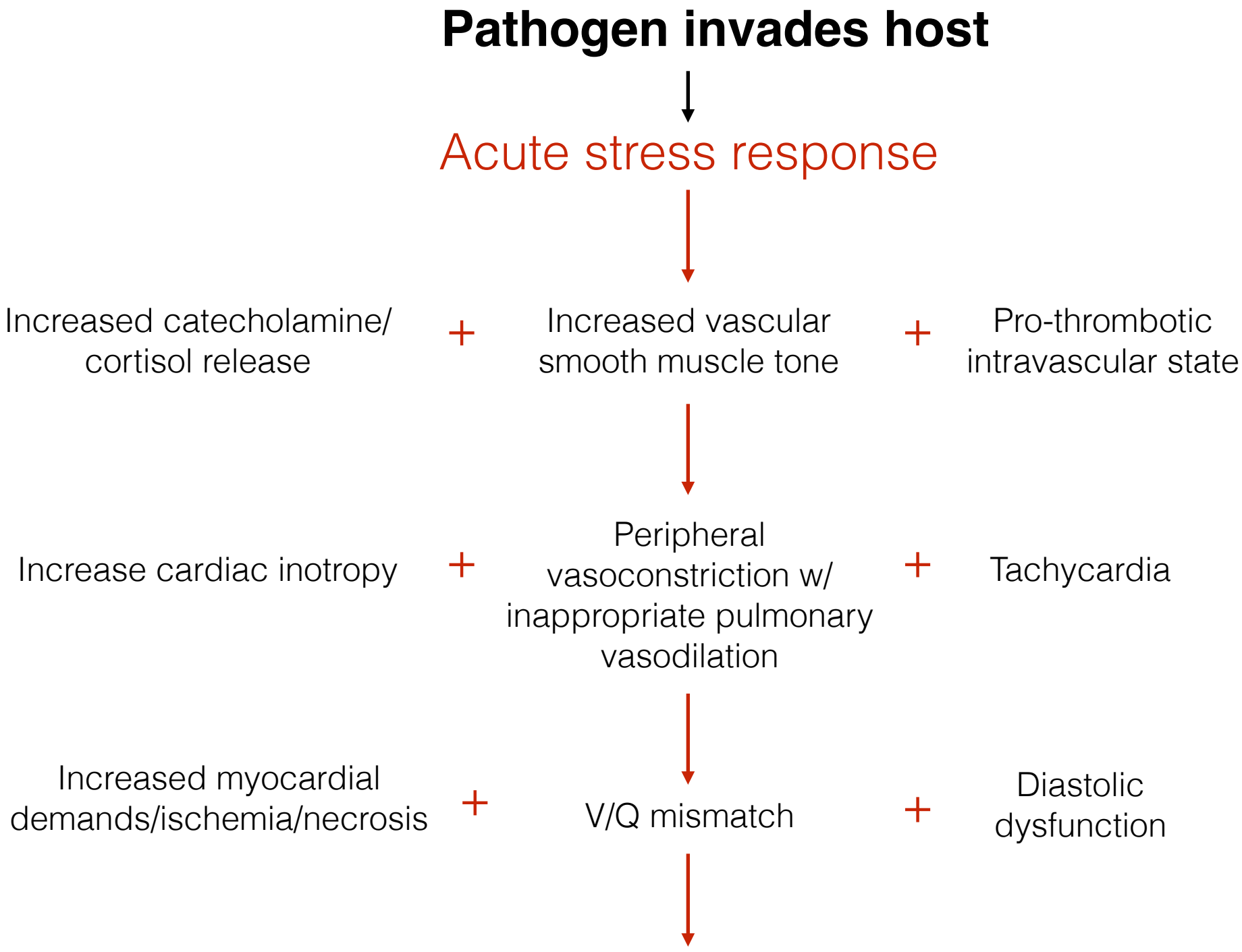
*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.

Sepsis

- **Multi-system disorder**
  - Cardiac depression with impaired LV function in up to 60% of patients

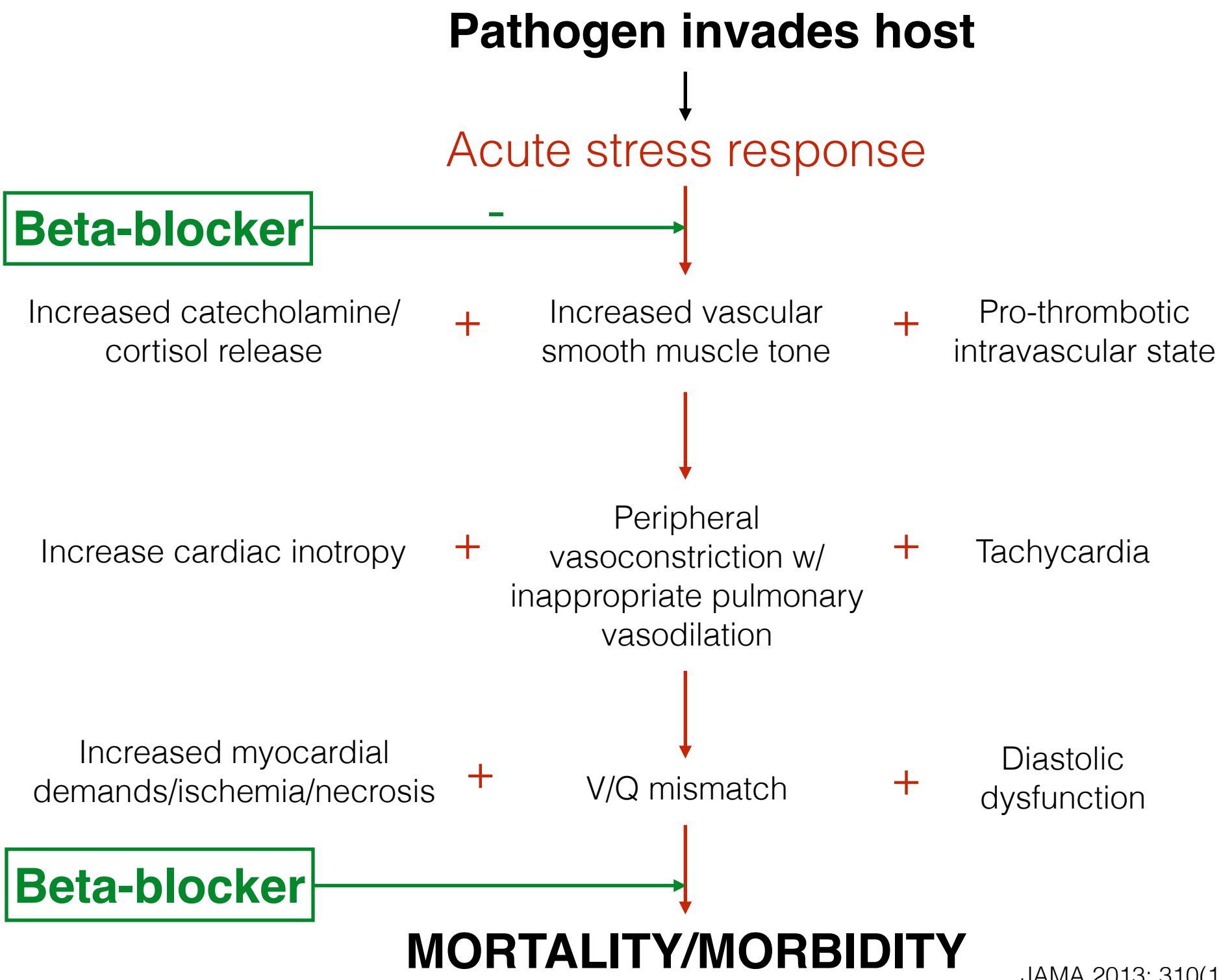
Crit Care Med 2010; 38[Suppl.]:S608 –S612



JAMA 2013; 310(16):1677-8

Enter beta-blockers

- Hypertension
- Acute coronary syndromes
- Ischemic Heart Disease
- Arrhythmias
- Cardiomyopathies
- Cirrhosis
- Thyroid disorders
- Valvular heart disease
- Septic shock



JAMA 2013; 310(16):1677-8

Beta-blockers

- Hypertension
- Acute coronary syndromes
- Ischemic Heart Disease
- Arrhythmias
- Cardiomyopathies
- Cirrhosis
- Thyroid disorders
- Valvular heart disease
- **Septic shock?!**

Clinical Question

P	In patients with septic shock…
I	… does beta-blockade…
C	…compared to standard therapy…
O	…improve ***outcomes***?

Outcomes

Mortality	**All-cause, sepsis-related** @ 28 days, 90 days, 1 year
Morbidity	**Length of stay** (hospital/ICU) **End-organ damage** (ventilator, renal replacement, vasoactive agents
Normalize surrogate markers	Goal MAP, CVP, lactate, ScVO

Search Strategy

Search terms	Beta-blocker (metoprolol, esmolol, labetaolol, propranolol), sepsis, severe sepsis, septic shock
Search Engines	Google Scholar, MEDLINE, EMBASE, IPA, WHO ICTRP
Limits	Adult humans, English

Results

Systematic Review	**None**
RCTs	**Morelli et al. 2013** Morellie et al. 2013 (pilot)
Observational (Cohort studies Chart review/ Case series)	**Macchia et al. 2012** **Gutierrez et al. 2009**
	Berk et al. 1970 Gore et al. 2006 Schmittinger et al. 2008
Ongoing trials	**None**

Gutierrez et al. 2009

Effect of beta blockers on sepsis outcome

Jose Gutierrez[1,2ABDEFG], Hossam Amin[1A], Roxana Lazarezcu[1B], El Kay[1B], Tatjana Rundek[2CDE]

[1] Department of Medicine, New York Medical College, Valhalla, NY, U.S.A.
[2] Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, U.S.A.

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

- Early vs. late sepsis
- Conflicting data between animal models
- Scarcity of human data
- **Objectives**:
  - Investigate association between “BB” treatment and mortality
  - Outcomes associated with changes in lactate

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

D	Retrospective chart review; adult MICU in NYC hospital	
P	Patient w/ sepsis (SIRS + infection); excluded those on vasopressors	
I/C	Data: sex, age, **BB administration (Y/N) during the 3 first days of MICU admission**, APACHE IV score, APS score, predicted mortality and the presence of CV RFs (CAD, LVD or SVT)	
O	**1º: Mortality**	2º: Δ lactate level (admission - "2nd sample"); **survival to discharge to ward**
S	Data obtained from first 3 days of MICU admission; descriptive statistics; categorical (Fisher exact); continuous (equal variance two-sample t-test); univariate/multivariate regression?	
T	July 2006-June 2007	

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

	Not exposed (N=xx) 54	Exposed (N=xx) 29	p value
Age Mean/SD Range	53.63/17.91 19–96	58.90/16.70 22–90	0.19487
Sex Males N (%) Females	26 (48.15) 28 (51.85)	15 (51.72) 14 (48.28)	0.8201
Smoking N(%)	10 (18.52)	7 (24.14)	0.5770
Diabetes Mellitus N(%)	20 (37.04)	12 (41.38)	0.8138
Hypertension N(%)	24 (44.44)	24 (82.76)	0.0010
Dyslipidemia N(%)	9 (16.67)	8 (27.59)	0.2645
CVA/PAD*	3 (5.56)	5 (17.24)	0.1205
APACHE** Mean (SD) Range	73.67 (23.21) 32–110	75.93 (23.47) 40–136	0.6741
APS*** Mean(SD) Range	60.35 (20.41) 21–99	63.34 (18.88) 34–108	0.5153
PM# Mean(SD) Range	23.50 (17.74) 1.2–64	21.84 1.7–76.4	0.6827

* Cerebrovascular accident/peripheral artery disease; ** acute physiology and chronic health evaluation score; *** acute physiological score;
# predicted mortality in percentage.

CAD **6% versus 45%**

Gutierrez et al. 2009

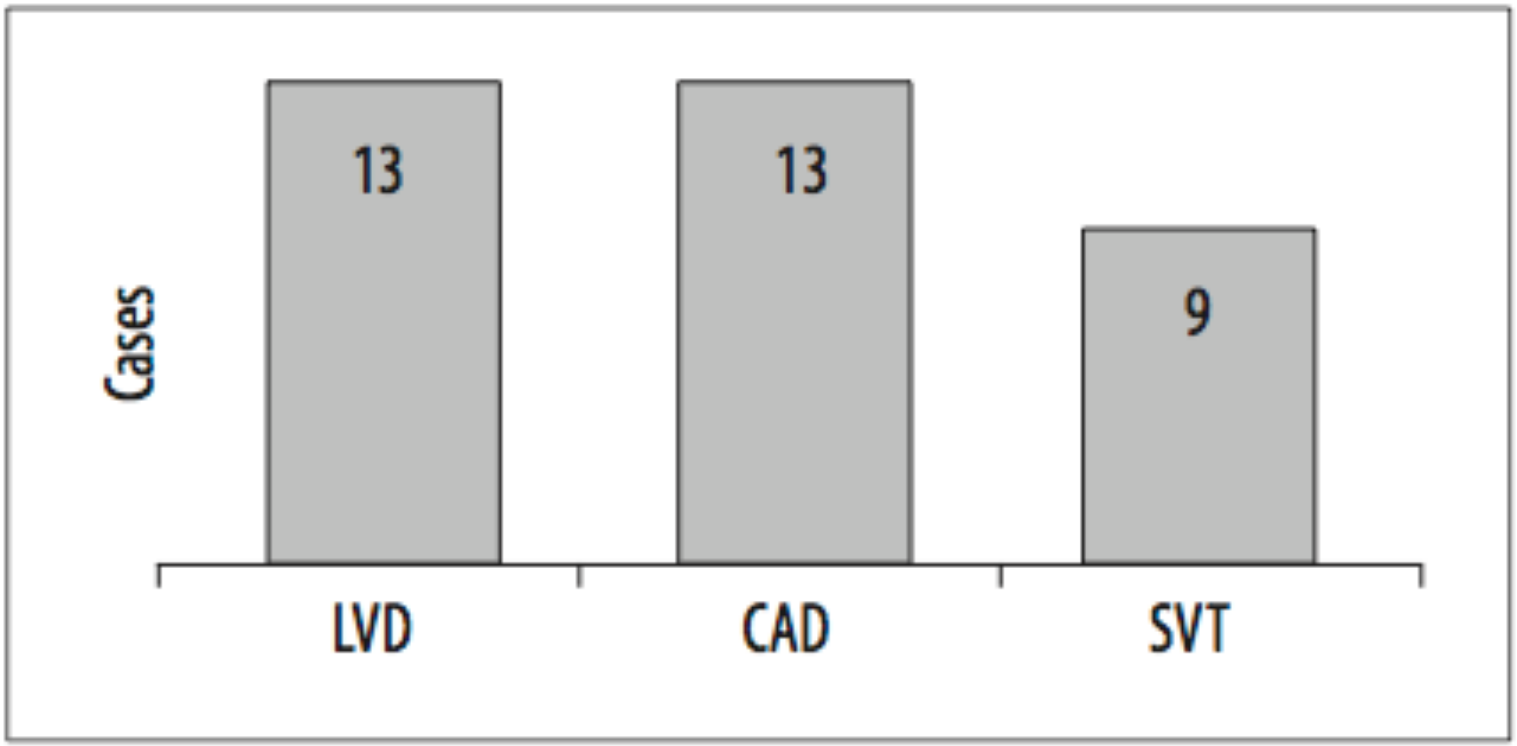


Figure 1. Indications for beta blockers.

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

BB use

Univariate analysis
OR=1.83
(95% CI 0.59–5.69)

Multivariate analysis
OR=1.843
(95% CI 0.56–6.10)

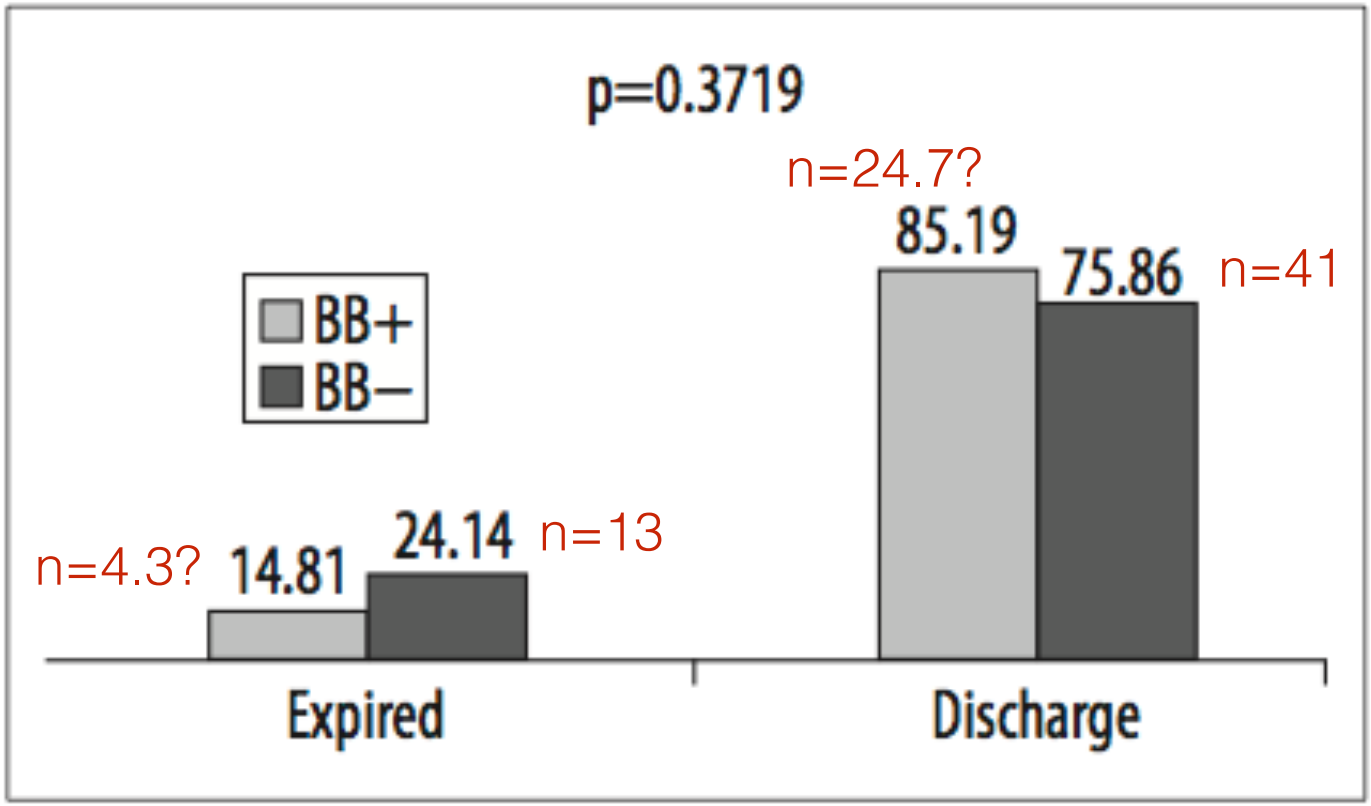


Figure 3. Outcome (%).

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

- *"This warrants further studies but extra precautions should ocurred when administering beta-blockers to severely ill patients who try to physiologically compensate the sepsis-induced hypermetabolism."*

Med Sci Monit, 2009; 15(10): CR499-503

Gutierrez et al. 2009

Strengths	☑ …
Limitations	☐ Retrospective, observational design ☐ Small sample size ☐ Unclear methods around regression analysis ☐ Lack of pertinent data (e.g. vital signs, concomitant interventions, antimicrobial appropriateness) ☐ Poorly prepared manuscript; missing statistical methods *had been and then, we did not made any subsequent evaluation of the patient hospital course.*

Macchia et al. 2012

Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis*

Alejandro Macchia, MD; Marilena Romero, PhD; Pablo Dino Comignani, MD; Javier Mariani, MD; Antonio D'Ettorre, PhD; Nadia Prini, MD; Mariano Santopinto, MD; Gianni Tognoni, MD

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

- Conflicting results among preclinical studies of beta blockers in different models of sepsis
- Clinical data composed largely of small, uncontrolled case series
- **Objectives**:
  - Evaluate association of previous beta-blocker prescription on short-term outcomes in ICU admitted patients with sepsis/septic shock

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

D	Retrospective observational cohort study; databases (hospital, Rx, ambulatory) = 12% Italian population
P	Consecutive patients with dx of sepsis (ICD code) admitted directly to ICU from ED or <48 hours transfer from other hospital
I/C	BB definition = >3 Rx fills in 4 month period before hospitalization
O	28 day survival from ICU admission
S	Logistic regression (univariate and multivariate) adjusting for: age, sex, hx of [HTN, dyslipidemia, DM, MI, CHF, AF, COPD, depression, cancer]
T	Hospitalizations between 2003-2008

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

- **Sensitivity analysis:**
  - Subgroup analysis (age, sex, co-morbidities)
  - Propensity score (PS) matching

Macchia et al. 2012

n=9465

Table 1. Demographic and clinical characteristics of the study population

Variable	All Patients	β-Blockers	No β-Blockers	*p*
N (%)	9465 (100)	1061 (11.2)	8404 (88.8)	
Demographic and baseline conditions				
Male, n (%)	4565 (49.6)	522 (49.2)	4186 (49.8)	.720
Age, mean (SD)	72.0 (12.8)	72.0 (10.6)	72.0 (13.0)	.961
Hypertension, n (%)	4880 (51.6)	862 (81.2)	4018 (47.8)	<.001
Dyslipemia, n (%)	1039 (11.0)	293 (28.2)	746 (8.9)	<.001
Diabetes, n (%)	2321 (24.5)	343 (32.3)	1978 (23.5)	<.001
Prior congestive heart failure, n (%)	1771 (18.7)	438 (41.3)	1333 (15.9)	<.001
Prior atrial fibrillation, n (%)	602 (6.4)	129 (12.2)	473 (5.6)	<.001
Prior myocardial infarction, n (%)	107 (1.1)	43 (4.1)	64 (0.8)	<.001
Chronic obstructive pulmonary disease, n (%)	1522 (16.1)	157 (14.8)	1365 (16.2)	.249
Depression, n (%)	990 (10.5)	140 (13.2)	850 (10.1)	.003
Malignancy, n (%)	1947 (20.6)	194 (18.3)	1753 (20.9)	.053
In-hospital characteristics and severity				
No organ dysfunction	6970 (73.6)	734 (69.2)	6236 (74.2)	.001
One organ dysfunction	2140 (22.6)	295 (27.8)	1845 (22.0)	<.001
Two organ dysfunction	308 (3.3)	28 (2.6)	280 (3.3)	.23
≥3 organ dysfunction	47 (0.5)	4 (0.4)	40 (0.5)	.56

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

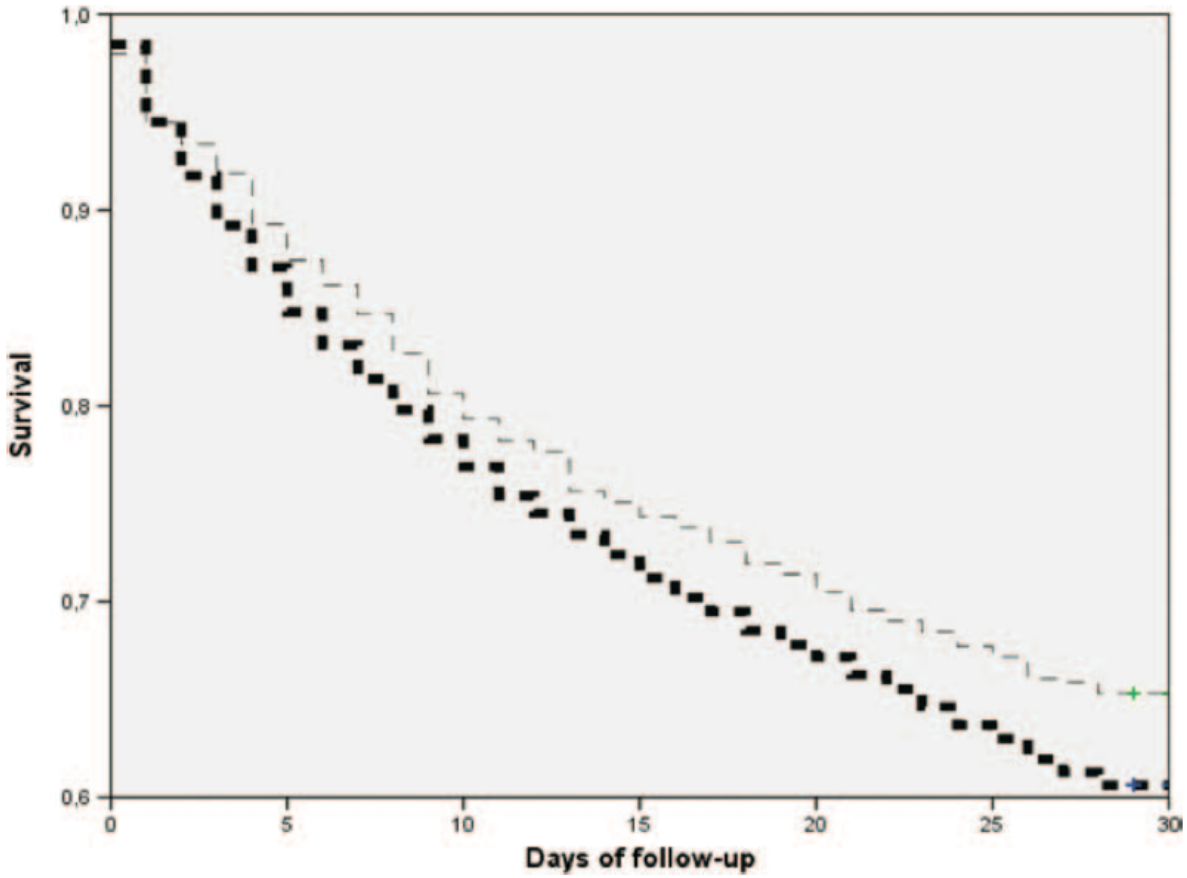


Figure 1. Survival plot for 28-day mortality.

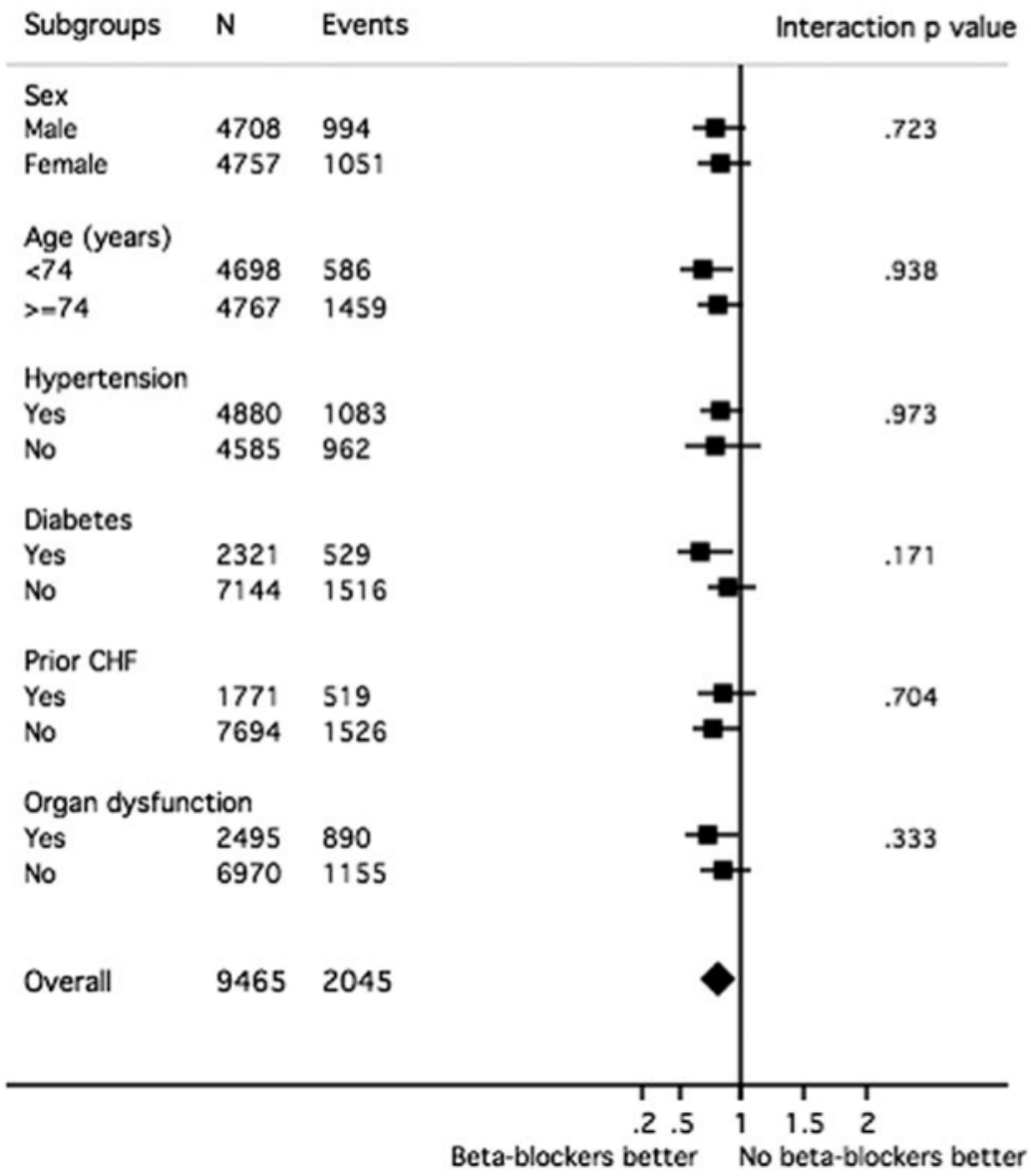
188/1061 (17.7%) vs. 1857/8404 (22.1%) fatal events;

Unadjusted OR 0.78 (95% CI 0.66–0.93; p = .005)

Adjusted OR 0.81 (95% CI 0.68–0.97; p = .025)

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012



Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

Table 2. Demographic and clinical characteristics of the propensity score–matched population

Variable	β-Blockers	Control	*p*
N (%)	995	995	
Male, n (%)	481 (48.3)	446 (44.8)	.116
Age, mean (SD)	72.5 (10.5)	72.9 (11.5)	.489
Hypetension, n (%)	802 (80.6)	825 (82.9)	.182
Dyslipemia, n (%)	246 (24.7)	232 (23.3)	.463
Diabetes, n (%)	314 (31.6)	305 (30.7)	.663
Prior congestive heart failure, n (%)	394 (39.6)	381 (38.3)	.550
Prior atrial fibrillation, n (%)	112 (11.3)	106 (10.7)	.667
Prior myocardial infarction, n (%)	25 (2.5)	18 (1.8)	.280
Chronic obstructive pulmonary disease, n (%)	149 (15.0)	133 (13.4)	.304
Depression, n (%)	129 (13.0)	153 (15.4)	.123
Malignancy, n (%)	185 (18.6)	167 (16.8)	.290

995 (of 1061) PS matched to control 1:1
182 (18.3%) vs. 233 (23.4%) fatal events
OR 0.72 (95% CI 0.57–0.91; p = .004)

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

- *"…our data support the hypothesis that previous prescription of β-blockers may confer a survival advantage to patients who later develop sepsis… (and)… should guide clinical decision to move forward to conduct well-designed, prospective clinical trials testing the effectiveness of this strategy in clinical practice."*

Crit Care Med 2012; 40:2768–2772

Macchia et al. 2012

Strengths	☑ Use of comprehensive databases ☑ Use of "hard", clinically relevant outcome ☑ Appropriate scenario for use propensity scores ☑ Reasonable methods to increase "confidence" in data (regression, sensitivity analyses)
Limitations	☐ Limited information re: prognostic variables for mortality in sepsis (severity of organ dysfunction, appropriateness of antibiotics, source/pathogen of sepsis, etc) ☐ Statistical analyses relies heavily on ICD coding ☐ Prescription fill ≠ therapeutic effect ☐ Generalizability to North America (Italian population)

Morelli et al. 2013

Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

JAMA 2013;310(16):1683-169

Morelli et al. 2013

- ⬆ plasma catecholamine levels & ⬆ HR = poorer outcomes
- Case series previously reported “good safety profile” (33% mortality; APS score = 53) with PO metoprolol + milrinone
- **Hypothesis**: IV beta-blocker titrated to HR control = effective approach to improving cardiac function and outcomes

JAMA 2013;310(16):1683-169

Morelli et al. 2013

D	Single-centre, P, OL, RCT; Italy
P	**Inclusion**: Septic shock (on NE) + HR >95 bpm **Exclusion** valve disease, pregnancy
I/C	**Esmolol IV infusion** @ 25mg/hr titrated q 20 min (by 50mg/hr increments) to achieve HR target <95 bpm vs. control
O	**1º:** % achieved in HR <95 bpm and >80 bpm over 96 hour
	2º: Hemodynamic and organ function measures, NE doses @ 24, 48, 72 and 96 hr; mortality @ 28 days
S	Sample size calculation: 64 in each group (20% change in HR, 80% power with 2-sided t-test) ITT; AUCs of continuous variables compared (to avoid multiplicity) 28 day mortality with Cox regression
T	July 2006-June 2007

JAMA 2013;310(16):1683-169

Morelli et al. 2013

Table 1. Baseline Characteristics of the Study Patients

	Esmolol (n = 77)	Control (n = 77)
Age, median (IQR), y	66 (52-75)	69 (58-78)
Men, No. (%)	54 (70)	53 (69)
Body mass index, median (IQR)[a]	29 (26-33)	28 (25-32)
SAPS II score, median (IQR)[b]	52 (47-60)	57 (49-62)
Norepinephrine dosage, median (IQR), μg/kg/min	0.38 (0.21-0.87)	0.40 (0.18-0.71)
Arterial lactate, median (IQR), mmol/L	1.5 (1.1-2.7)	1.9 (1.1-3.1)
Platelet count, median (IQR), × 10^3/μL	178 (126-272)	129 (73-206)
Fluid input, mL, 24 h prior to inclusion, median (IQR),	4700 (4300-5200)	4800 (4100-5325)
Cause of septic shock, No.		
Necrotizing fasciitis	1	2
Pyelonephritis	1	1
Peritonitis	21	30
Pneumonia	54	44

Pathogens, No. (%)	Esmolol	Control
Klebsiella spp	29 (38.0)	20 (26.0)
Acinetobacter spp	6 (7.8)	6 (7.8)
Acinetobacter spp + *Klebsiella* spp	11 (14.3)	8 (10.4)
Staphylococcus aureus	6 (7.8)	6 (7.8)
Escherichia coli	3 (3.9)	8 (10.4)
Pseudomonas spp	5 (6.5)	4 (5.2)
Aspergillus spp	0 (0.0)	3 (3.9)
Others	17 (22.0)	22 (28.6)
Preexisting conditions, No. (%)		
Coronary artery disease	25 (32.5)	21 (27.3)
Congestive heart failure	11 (14.3)	13 (16.9)
Chronic kidney disease	5 (6.5)	4 (5.2)
Chronic obstructive pulmonary disease	16 (20.8)	20 (26.0)

JAMA 2013;310(16):1683-169

Morelli et al. 2013

	24 hours	48 hours	72 hours	96 hours	AUC	p-value
Fluid infusion, mL/24 h						
Esmolol	5000 (4300 to 5400)	4600 (4300 to 5000)	4300 (4000 to 4600)	4000 (3600 to 4300)	3975 (3663 to 4200)	<.001
Control	5200 (4700 to 5800)	5400 (4900 to 5700)	5200 (4800 to 5600)	5400 (4725 to 6000)	4425 (4038 to 4775)	

JAMA 2013;310(16):1683-169

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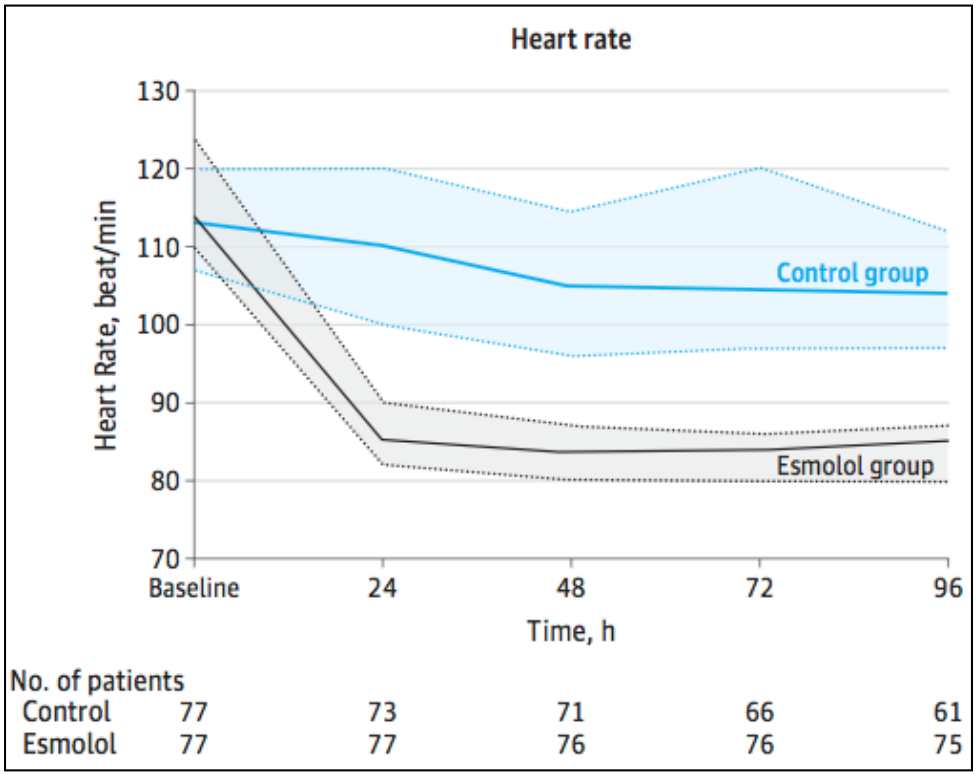
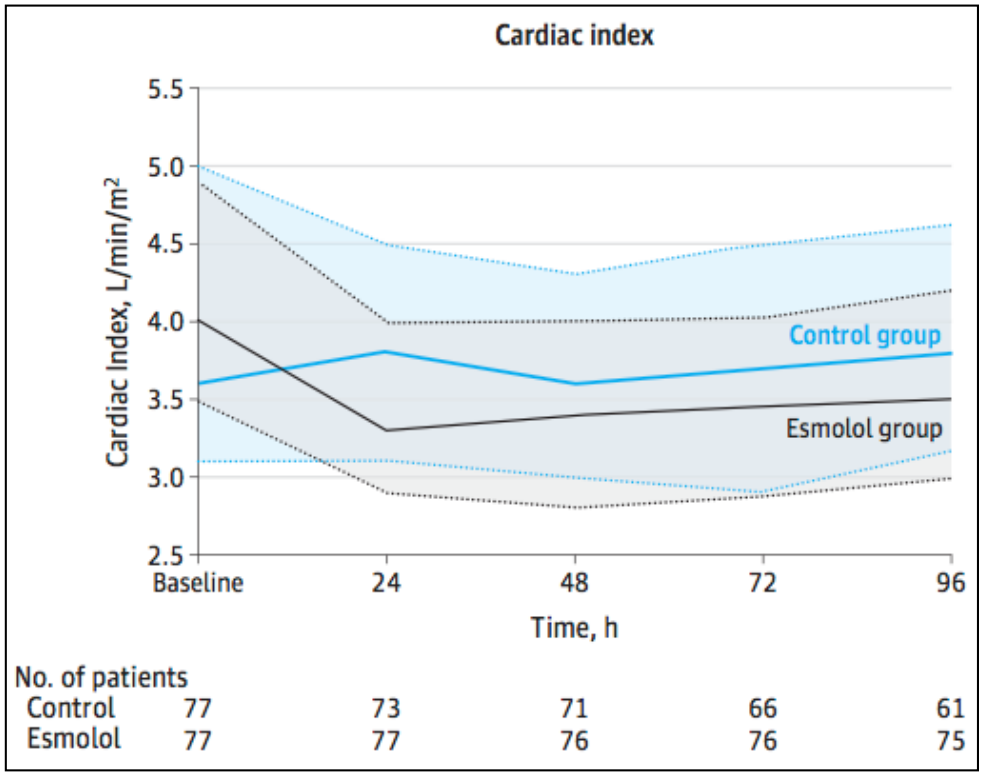
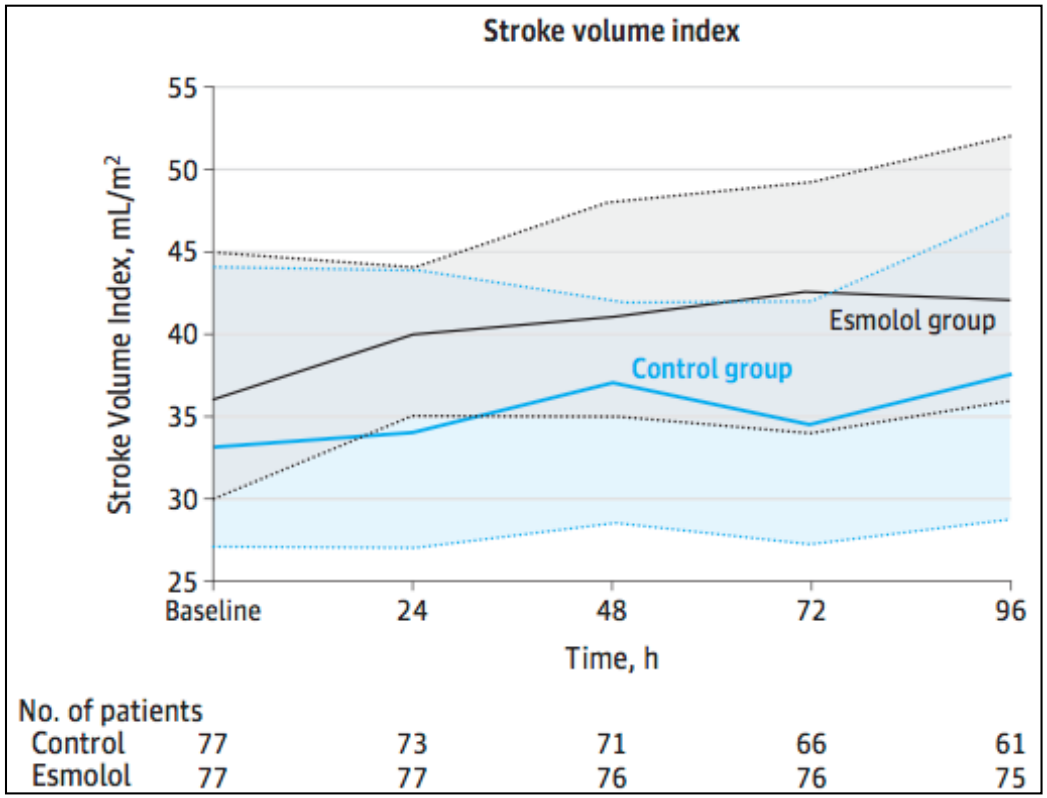
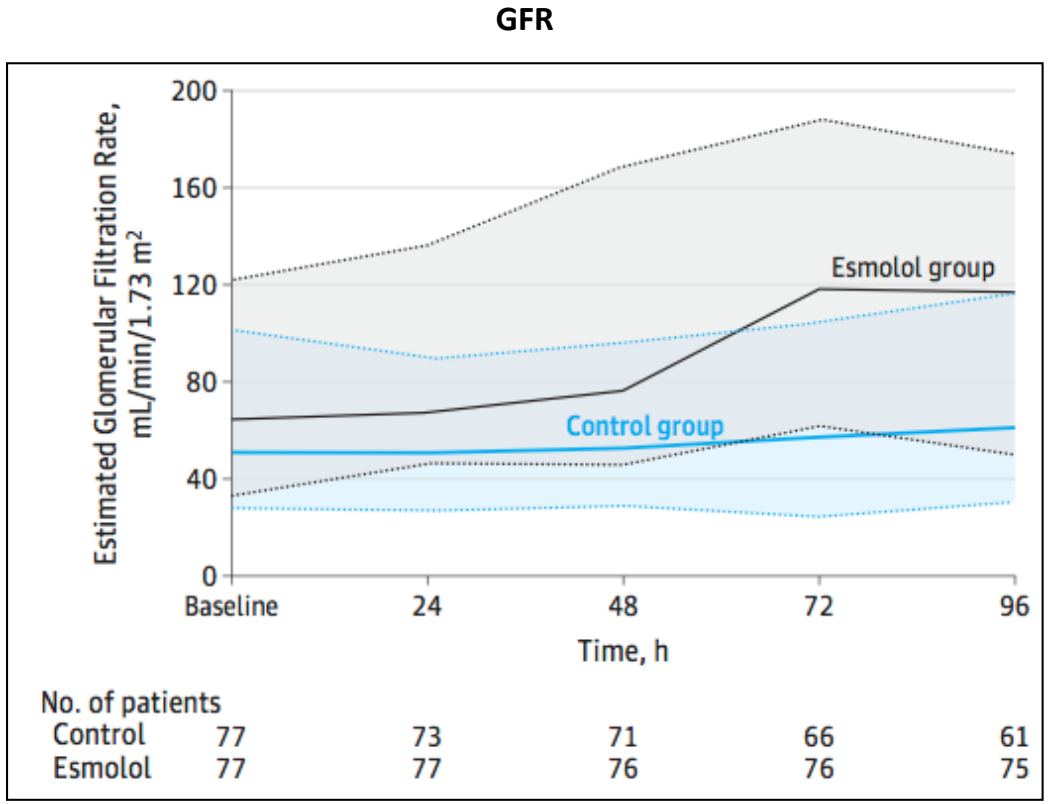




JAMA 2013;310(16):1683-169

Morelli et al. 2013





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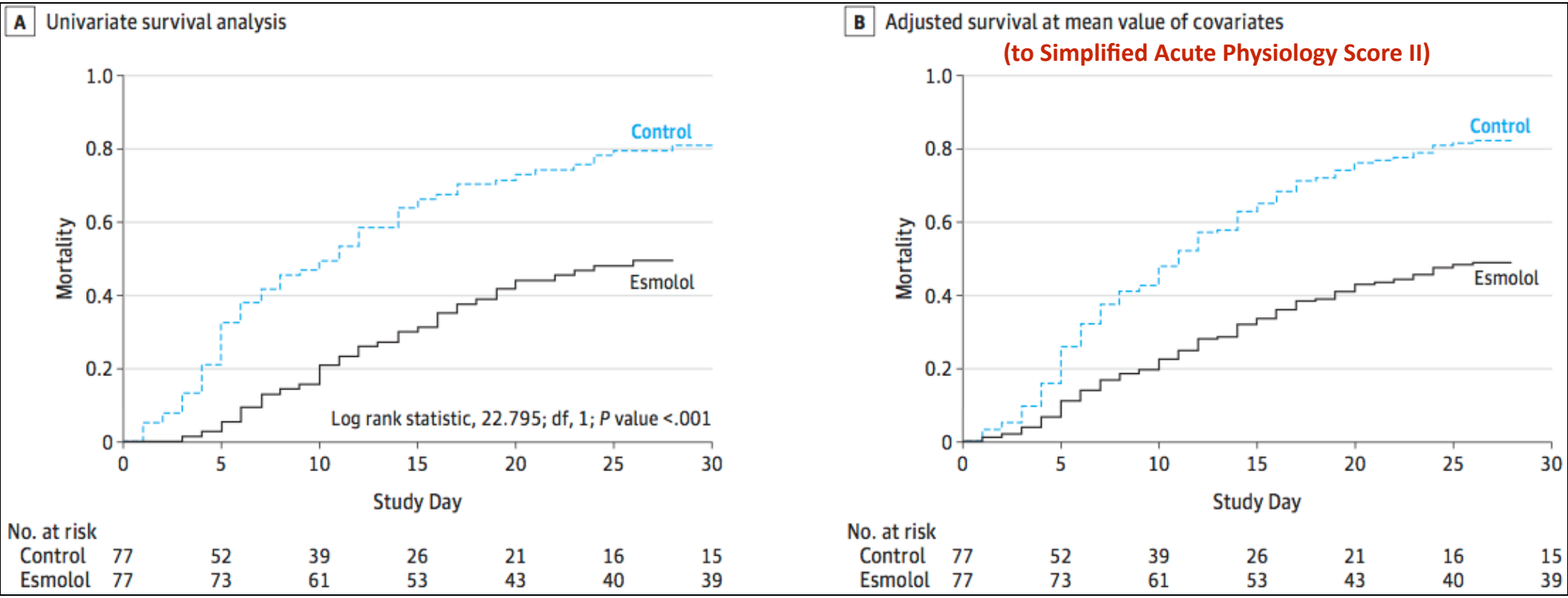

JAMA 2013;310(16):1683-169

Morelli et al. 2013

Table 3. Outcome Data of Study Patients

Outcome	No. (%) Esmolol (n = 77)	Control (n = 77)	ARR/NNT	*P* Value
Mortality				
28 d	38 (49.4)	62 (80.5)	31.1% / 3	<.001
ICU	44 (57.1)	68 (88.3)	31.2% / 3	<.001
Hospital	52 (67.5)	70 (90.9)	23.4% / 4	<.001
Length of ICU stay, d				
Median (IQR)	19 (11-27)	14 (7-25)	+5 days	.03
Survivors', median (IQR)	17 (9-28)	21 (11-34)		.70
Cause of death, No./total, (%)				
Multiple organ failure	15/52 (28.8)	26/70 (37.1)		
Refractory hypotension	32/52 (61.6)	44/70 (62.9)		.71
Unknown cause	5/52 (9.6%)			

JAMA 2013;310(16):1683-169

Morelli et al. 2013

- *"For patients in septic shock, the open-label use of esmolol was able to achieve reductions in heart rate to target levels, without an increase in adverse outcomes compared with standard treatment. Further investigation of the effects of esmolol on clinical outcomes is warranted."*

JAMA 2013;310(16):1683-169

Morelli et al. 2013

Strengths	☑ Experimental study design ☑ Complete report of data ☑ Accounted for severity of illness and fluid administration (non-placebo)
Limitations	☐ Small, single-centre study ☐ High mortality rates (~90% vs. SAPS II predicted 50%) & NE use ☐ Generalizability to North America (Italian) and lower risk patients ☐ Generalizability of intervention (HR target? Or something else…?)

JAMA 2013;310(16):1683-169

Summary

- Represents potential paradigm shift in sepsis pathophysiology and management
- Requires specification of patient population(s) & clear definitions of intervention/target(s)

Conclusion

- **Do not recommend** as treatment alternative in patients with sepsis without clear indication for beta-blockade

Questions?