Safety and Efficacy of Hetastarch Solution for Fluid Resuscitation From Trauma

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No other financial relationships would constitute conflict of interest

An *"off label"* use of an FDA approved drug will be discussed

✳

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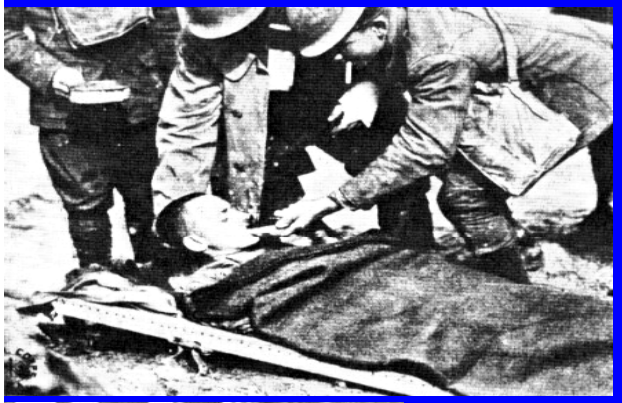
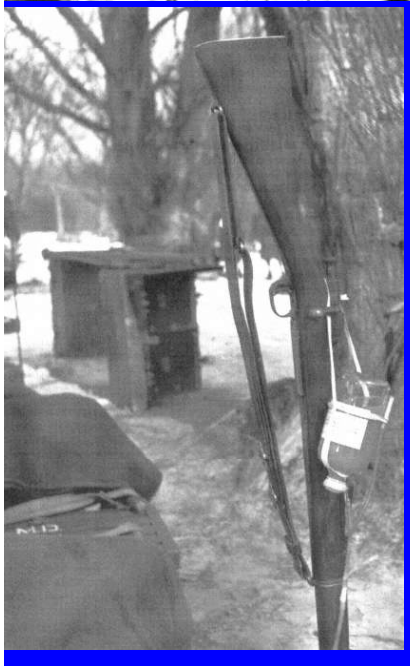
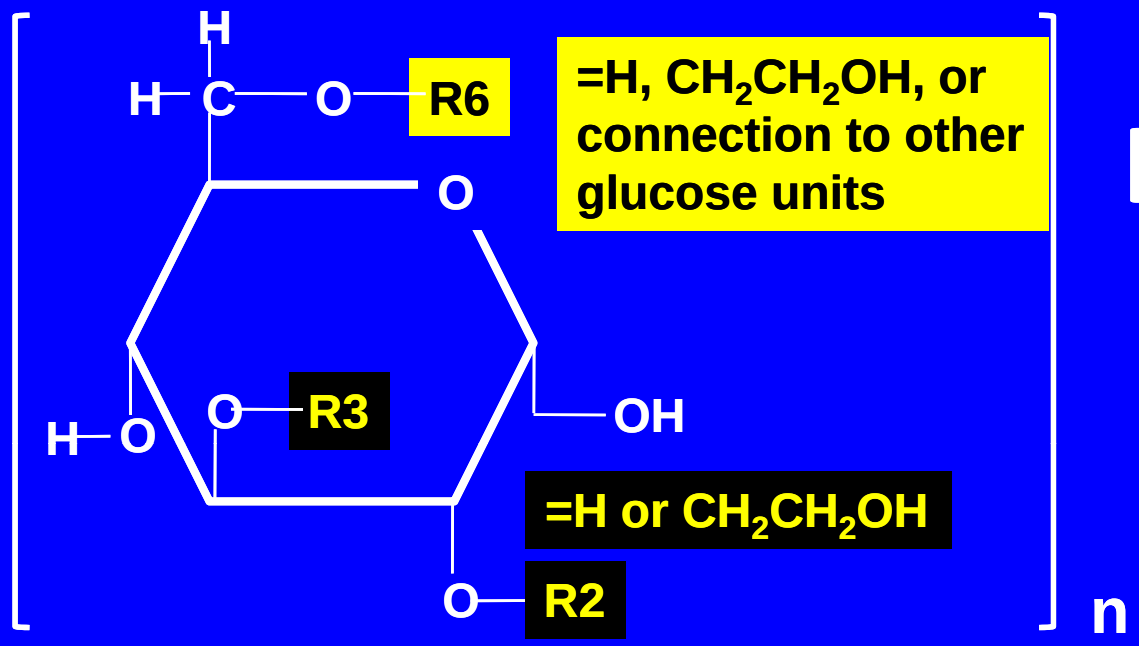


"…the greatest opportunity for reducing mortality and morbidity of battlefield casualties involves fluid resuscitation and treatment of hypovolemia…"



- **resuscitation changed little in 20th century**
- **IVF has changed even less**
- **battlefield logistics especially challenging**

Artificial colloids for hypovolemia?



Hetastarch

-Hydroxyethyl groups attached by ether linkage at C-2, C-3, & C-6 of the glucose unit

-0.75 molar substitution (75 hydroxyethyl groups for every 100 glucose units)

-avg MW = 670K (range =450-800K; >80% of the polymer units 20K- 2.5M)

Molar substitution, avg MW, & size distribution determine side effects (e.g. coag, anaphylaxis, etc)

http://www.hospira.com

Hextend™,

6% hetastarch
in lactated electrolyte injection

FDA approved (4/99) for hypovolemia

- **efficacy approximates that of 5% albumin**
- **side effect profile is favorable vs albumin**
- ***safety/efficacy <u>only in elective surgery</u>*** ✳

hetastarch replaced by plasma proteins;

π and electrolytes help retain intravascular volume

	Lactated Ringer's injection USP	Hextend, 6% hetastarch in lactated electrolyte injection	0.9% NaCl injection USP	Hespan, 6% hetastarch in 0.9% NaCl injection
mg %				
NaCl	600	672	900	900
Na lactate	310	317	0	0
KCl	30	22	0	0
$CaCl_2$	20	37	0	0
$MgCl_2$	0	9	0	0
Dextrose	0	99	0	0
Hetastarch	0	6000	0	6000
mEq/L				
Na	130	143	154	154
K	4	3	0	0
Ca	3	5	0	0
Cl	109	124	154	154
Lactate	28	28	0	0
Mg	0	0.9	0	0
mOsm	273	307	308	309

2003 May;54(5):S46-S51

The Journal of TRAUMA Injury, Infection and Critical Care

Fluid Resuscitation in Modern Combat Casualty Care: Lessons Learned from Somalia

COL John B. Holcomb, MD, FACS

"...One liter of LR expands volume by approx 250 mL;
500 mL of Hextend expands volume by 800 mL...
500 mL of Hextend is functionally equivalent to 3L of LR ..
<u>this represents a 6x weight/benefit advantage</u> ..."

<u>Concensus algorithm:</u>

"...After hemorrhage is controlled, 500 -1,000mL Hextend....."

The military has deployed Hextend for logistic reasons...

Is one liter safe and effective for trauma?

Hextend in humans (as of 7/1/09)

1) Blood loss in cardiac surgery. Transfusion. 2008Apr;48(4):768-75.

2) Case report: anaphylaxis. Can J Anaesth. 2006 Oct;53(10):989-93.

3) Plasma volume in volunteers. Anaesthesia. 2004 Aug;59(8):738-42.

4) Pharmacokinetics in volunteers. Anesth Analg. 2002 Mar;94(3):538-44;

5) Acid-base and electrolytes and gastric mucosal perfusion in elderly surgical patients. Anesth Analg. 2001 Oct;93(4):811-6.

6) Large volume use in major surgery: a randomized phase III clinical trial. Anesth Analg. 1999May;88(5):992-8.

plus at least 8 studies evaluating effects on coagulation ex vivo

but, no studies in trauma patients

2003 Jul;55(1):94-105 **ATACCC '00** The Journal of TRAUMA Injury, Infection and Critical Care

Novel resuscitation strategy for pulmonary contusion after severe chest trauma *ME Kelly, PR Miller, JJ Greenhaw, TC Fabian, KG Proctor*

2004 Sep;57(3):547-554 **ATACCC '02** The Journal of TRAUMA Injury, Infection and Critical Care

Building a better fluid for emergency resuscitation of traumatic brain injury *BA Crookes, SM Cohn, H Bonet, M Majetschak, EA Burton, J Nelson, AJ Varon, J Linden, KG Proctor*

2004 Aug;136(2):353-363 **ATACCC '04** SURGERY

Changes in intracranial pressure coagulation and neurologic outcome after resuscitation from experimental brain injury with hetastarch *DR King, SM Cohn, KG Proctor*

2007 Feb;204(2):261-275 **ATACCC '07** JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS

Cerebrovascular resuscitation after polytrauma and fluid restriction *SA Earle, MA deMoya, JE Zuccarelli, MD Norenberg, KG Proctor*

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

MP Ogilvie, BMT Pereira, MG McKenney, PJ McMahon, R Manning, AS Livingstone, N Namias, CI Schulman, & KG Proctor

Initial fluid resuscitation in trauma patients

Verified by University of Miami, Sep 2008
Clinical trials.gov identifier: NCT00527098

The purpose is to evaluate the safety and efficacy of HET sol'n (Hextend™) ± standard of care for resuscitation of trauma patients

Randomized blinded design is not permitted in Florida with waiver of consent *even when comparing two FDA-approved compounds*

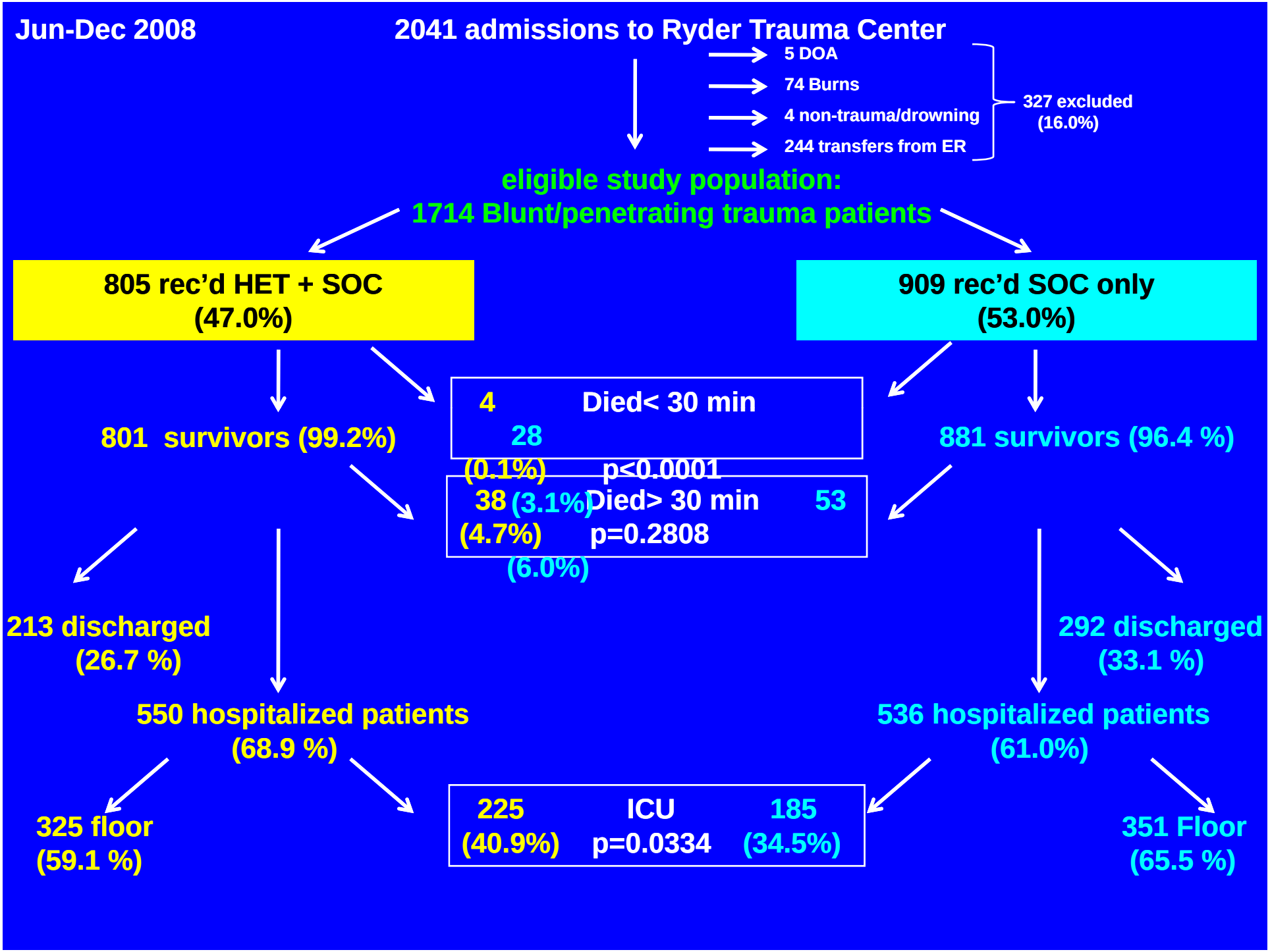
HET added to UM formulary in Apr 08

Available to all as therapeutic option

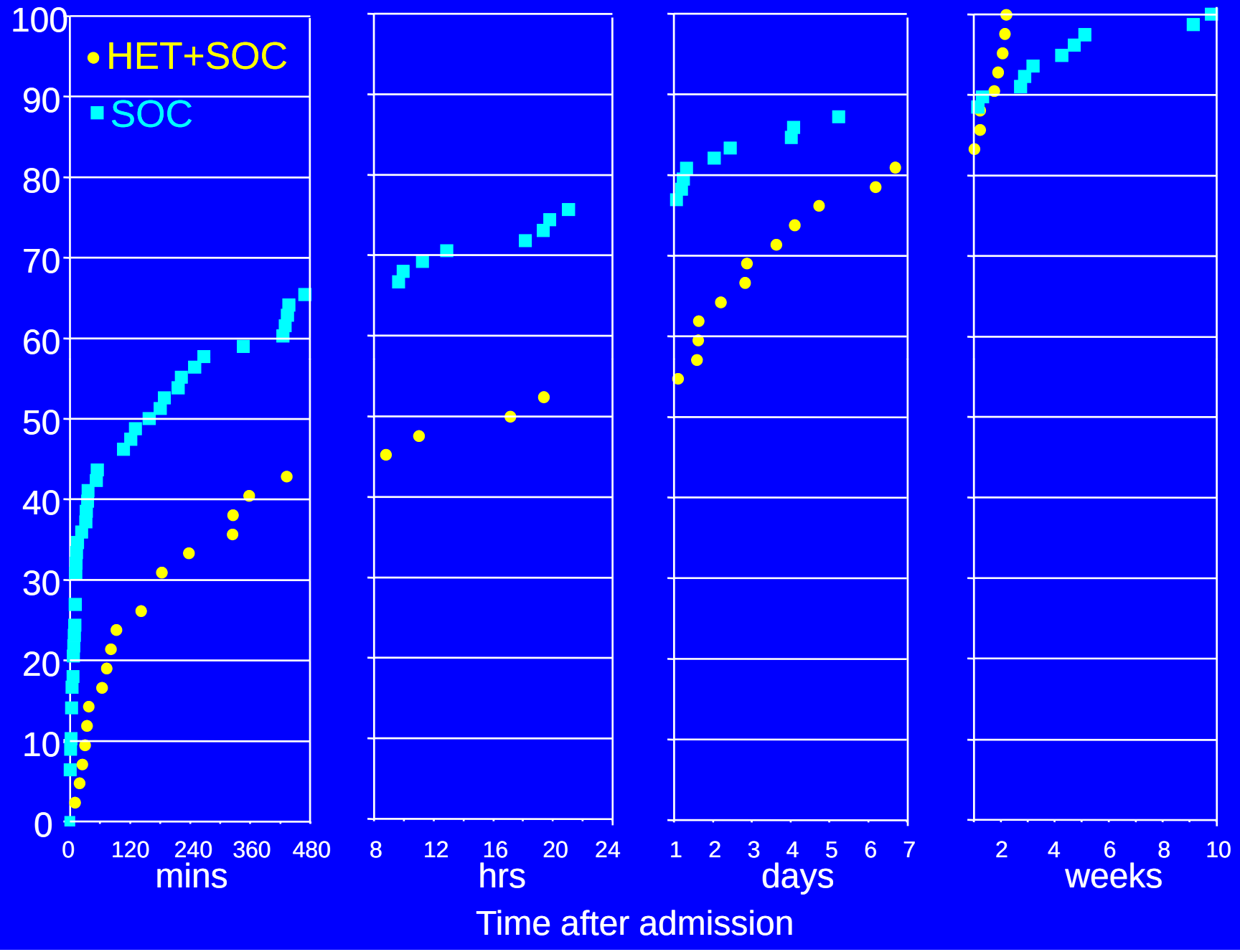
IRB approved to review initial clinical experience with waiver of consent

"A good plan today is better than a perfect plan tomorrow."

—George S. Patton.


Jun-Dec 2008
2041 admissions to Ryder Trauma Center
5 DOA
74 Burns
4 non-trauma/drowning
244 transfers from ER
327 excluded (16.0%)
eligible study population:
1714 Blunt/penetrating trauma patients
805 rec'd HET + SOC (47.0%)
909 rec'd SOC only (53.0%)
4 (0.1%)
Died< 30 min
28 (3.1%)
p<0.0001
801 survivors (99.2%)
881 survivors (96.4 %)
38 (4.7%)
Died> 30 min
53 (6.0%)
p=0.2808
213 discharged (26.7 %)
292 discharged (33.1 %)
550 hospitalized patients (68.9 %)
536 hospitalized patients (61.0%)
225 (40.9%)
ICU
185 (34.5%)
p=0.0334
325 floor (59.1 %)
351 Floor (65.5 %)

Cumulative mortality vs time

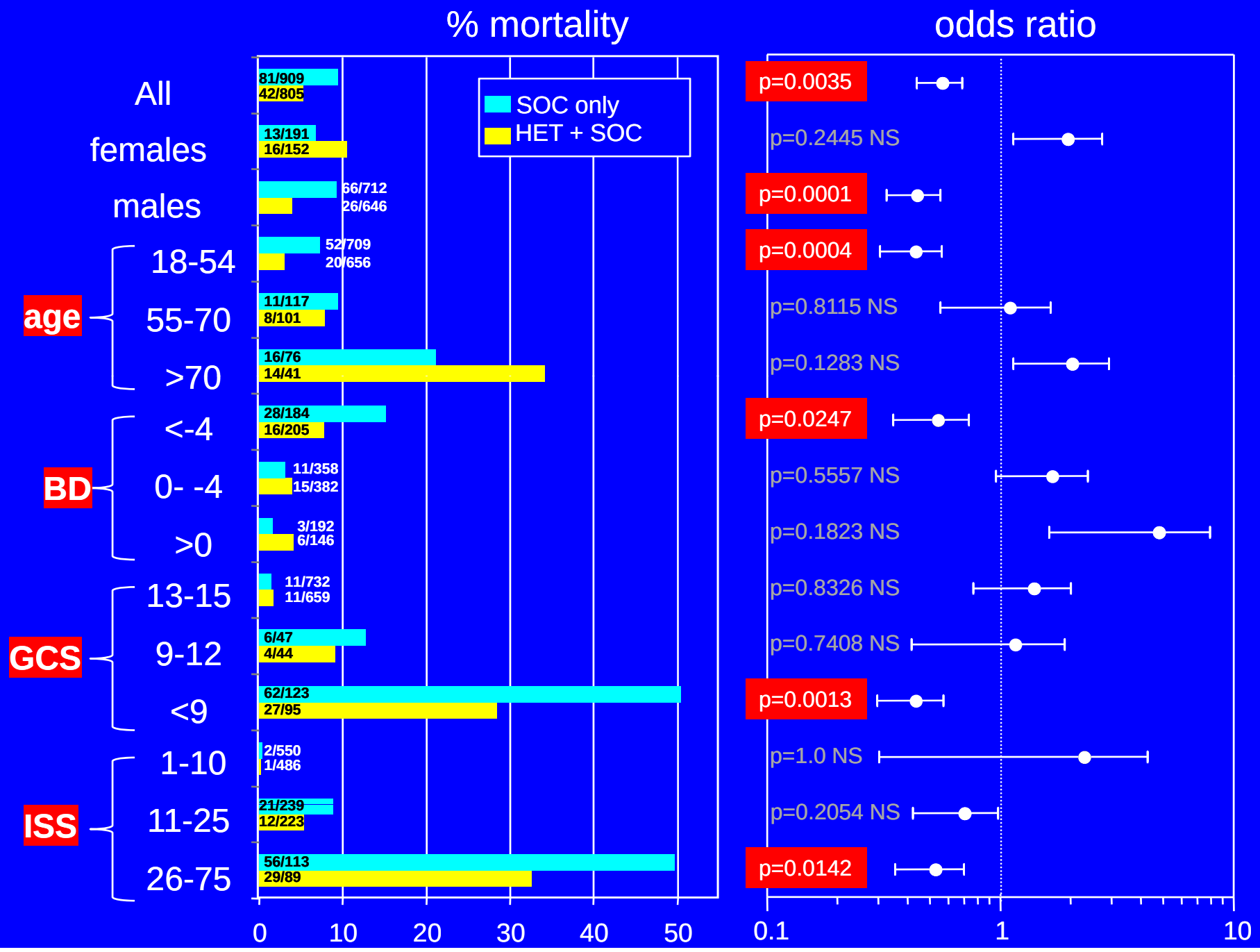


Causes of Death (Jun-Dec 2008) after blunt or penetrating trauma

	Hem shock	ARF	TBI	septic shock	ARDS
SOC (n=81)	49 60%	3 4%	21 26%	7 9%	2 2%
HET+SOC (n=42)	20 48%	4 10%	20 48%	11 26%	11 26%

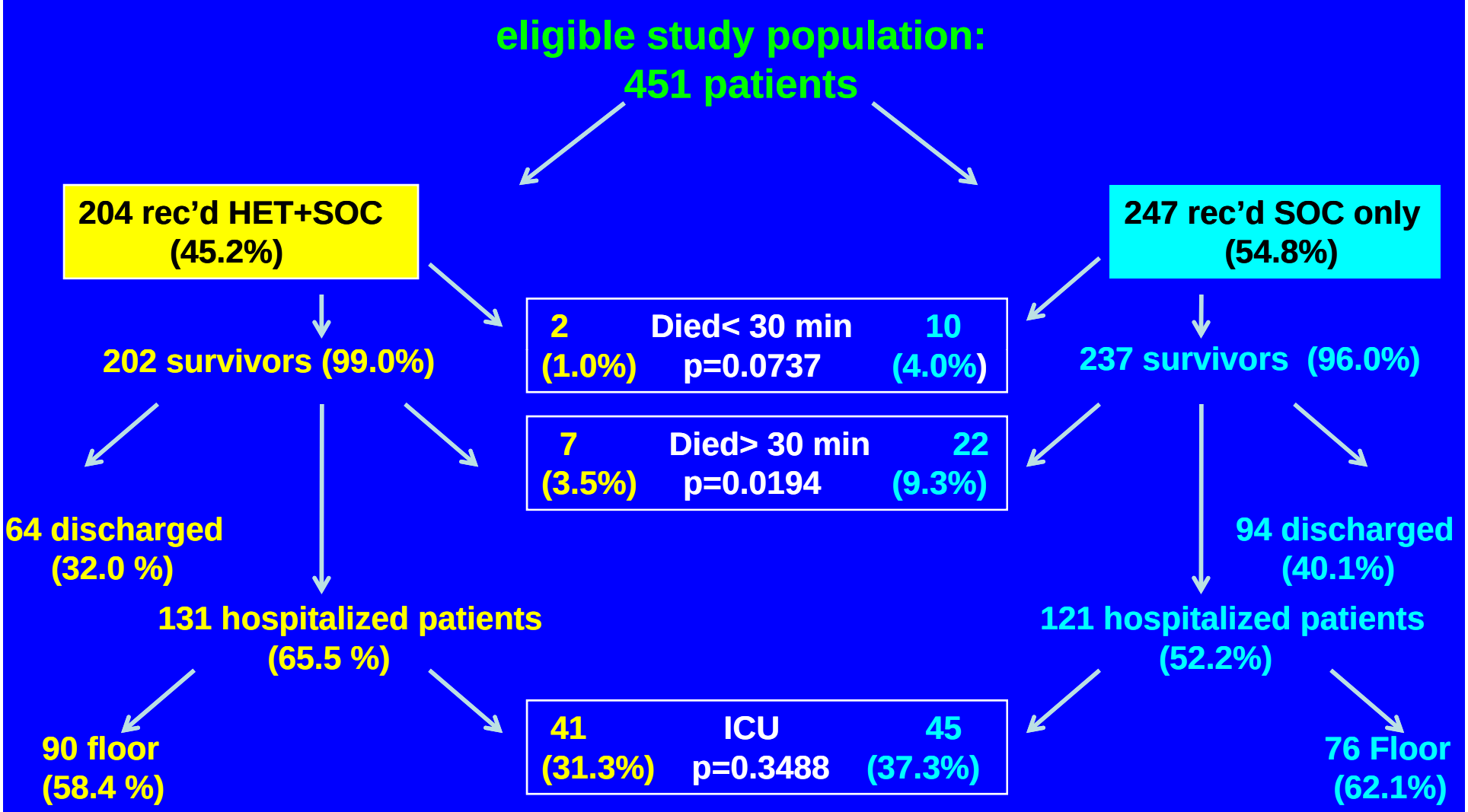
"... reduce mortality and morbidity by treatment of hypovolemia…"

Blunt or penetrating univariate analysis

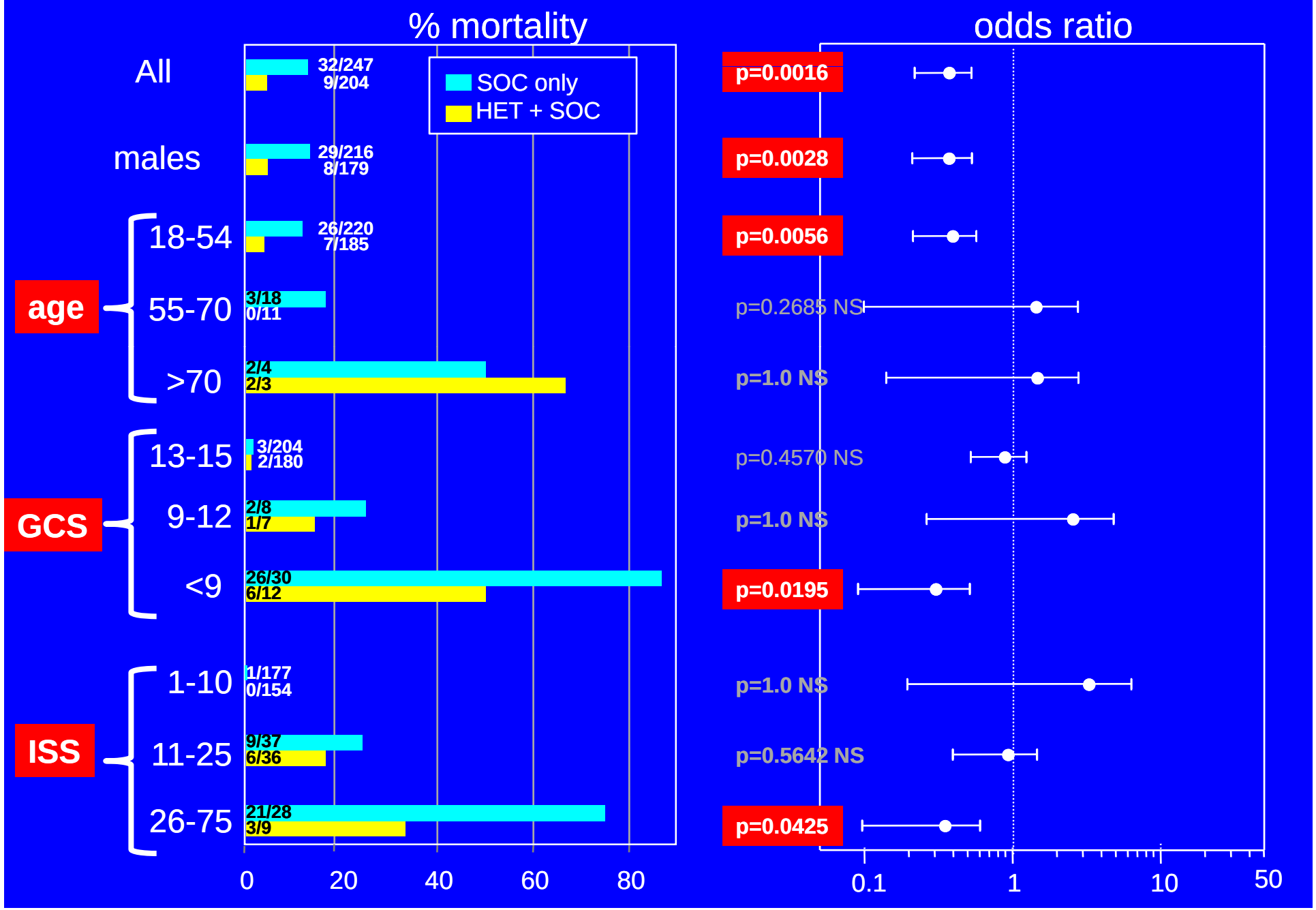


Admitted to ICU M±SD		HET+ SOC (n=227)	SOC (n=188)
	ISS	19±10	19±10
	RTS	6.9±1.4	7.1±1.1
	Survival probability	89.5±17.0	92.5±12.1
initial TRU lab values	BD, mEq/L	-5 ± 5	-3 ± 5
	Hct	38.4 ± 6.4	39.1 ± 6.2
	PT, sec	**14.0 ± 3.4**	**13.6 ± 4.2**
	PTT, sec	**25.9 ± 6.0**	**25.2 ± 6.0**
initial ICU lab values	BD, mEq/L	-1 ± 4	-2 ± 4
	Hct	35.0 ± 5.6	36.3 ± 10.3
	PT, sec	**14.8 ± 1.5**	**14.8 ± 2.9**
	PTT, sec	**30.6 ± 7.5**	**30.4 ± 8.4**
24 hr totals	pRBCs, units	7 ± 8	7 ± 6
	FFP, units	6 ± 7	7 ± 6
	IVF, ml	8126 ± 6355	7508 ± 5782
	UO, ml	3355 ± 1654	3093 ± 1848
LOS	ICU, days	14 ± 18	10 ± 14
	Hospital, days	25 ± 28	21 ± 23

PENETRATING TRAUMA ONLY



Penetrating trauma only univariate analysis



however with multi-variate analysis.....

Predictors of Mortality After Blunt or Penetrating Trauma (n=1699)

	Odds Ratio ±SE	p	95% CI
age	1.06 ± 0.01	<0.001	1.04 - 1.07
gender	2.09 ± 0.70	0.027	1.09 - 4.01
GCS	0.74 ± 0.02	<0.001	0.69 - 0.79
ISS	1.12 ± 0.01	<0.001	1.10 - 1.15
Penetr	6.53 ± 2.48	<0.001	3.11 - 13.72
HET	0.63 ± 0.19	0.117	0.35 - 1.12

multi-variate analysis.....

females, early deaths excluded....

Predictors of Mortality after Penetrating Trauma (n=430)

	Odds Ratio ±SE	p	95% CI
age	1.07 ± 0.03	0.020	1.01 - 1.14
GCS	0.62 ± 0.06	<0.001	0.52 - 0.75
ISS	1.17 ± 0.04	<0.001	1.09 - 1.26
HET	0.16 ± 0.16	0.068	0.02 - 1.14

Summary & Conclusions

Het + SOC for initial resuscitation

First in trauma pts; largest in surgical pts

No ↑coagulopathy; no ↑morbidity (safety)

Mortality possibly ↓* in extremis (efficacy)

*Open label, non-randomized, single center trial has inherent limitations...

Other studies vs SOC

1. 32 RCTs; no evidence that albumin ↓ mortality vs crystalloid Intern Emerg Med. 2006;1(3):243-5.

2. 55 RCTs; no evidence that any colloid ↓ mortality vs crystalloid Cochrane Database Syst Rev. 2007 Oct 17;(4):CD000567.

3. 70 RCTs; no evidence that any one colloid is safer or more effective than any other. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001319.

4. Large multicenter trial stopped in 2009 by NIH because interim results showed that hypertonic saline provides no survival benefit vs normal saline www.medscape.com/viewarticle/590647

Why??

Several differences in trial design and...

absence of proof is NOT proof of absence, but .....

its impossible to ignore previous RCTs

"at least" three explanations

→***chance*** ***(univariate p<0.01: multivariate 0.06<p<0.12)***

→***selection bias*** ***(not available in time?)***

→***true treatment effect***

-rapid volume correction for subset in extremis(?)

-negative effect of standard of care crystalloid(?)

Adequately powered RCT in patients *with severe injury* is necessary to reconcile these alternatives