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Beta-blockers in Traumatic Brain Injury: In or Out?

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Tucson, Arizona

USA

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Background

- Traumatic Brain Injury (TBI)
  - Significant cause of Trauma Mortality
- USA
  - 1.7 million head injuries
  - 1.4 million ED visits
  - 275,000 patients hospitalized
  - 50,000 deaths

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Background

- Beta-Blockers (BBs)
  - Improve mortality after trauma

The Journal of TRAUMA® Injury, Infection, and Critical Care

Beta-Blocker Use is Associated With Improved Outcomes in Adult Trauma Patients

Saman Arbabi, MD, MPH, Eric M. Campion, MD, Mark R. Hemmila, MD, Melissa Barker, RN, Mary Dimo, PharmD, Karla S. Ahrns, RN, Andreas D. Niederbichler, MD, Kyros Ipaktchi, MD, and Wendy L. Wahl, MD

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Background

- Beta-Blockers
  - Improve mortality after severe TBI

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care*

Beta-Blocker Exposure is Associated With Improved Survival After Severe Traumatic Brain Injury

Bryan A. Cotton, MD, Kimberly B. Snodgrass, PharmD, Sloan B. Fleming, PharmD, Robert O. Carpenter, MD, Clinton D. Kemp, BS, Patrick G. Arbogast, PhD, and John A. Morris, Jr., MD

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Background

- Riordan et al 2007
- Salim 2007
- Inaba et al 2008
- Friese et al 2008
- Schroeppel et al 2010, 2014

- ALL showed positive effects from BB
  - Some only in specific subgroups

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Beta-Blockers in TBI

- WARNING!!!

- UNPUBLISHED RESEARCH AHEAD

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Beta-Blockers

- No PUBLISHED Randomized Clinical Trial

A Prospective Randomized Study Comparing Metoprolol to Placebo in The Management of Severe Traumatic Brain Injury

Hassan A Abu Khaber [1, 2], Akram M Fayed [1, 2], Ahmed A Khattab [1, 2]

(1) Department of Critical Care Medicine, (2) Faculty of Medicine, University of Alexandria, Egypt.

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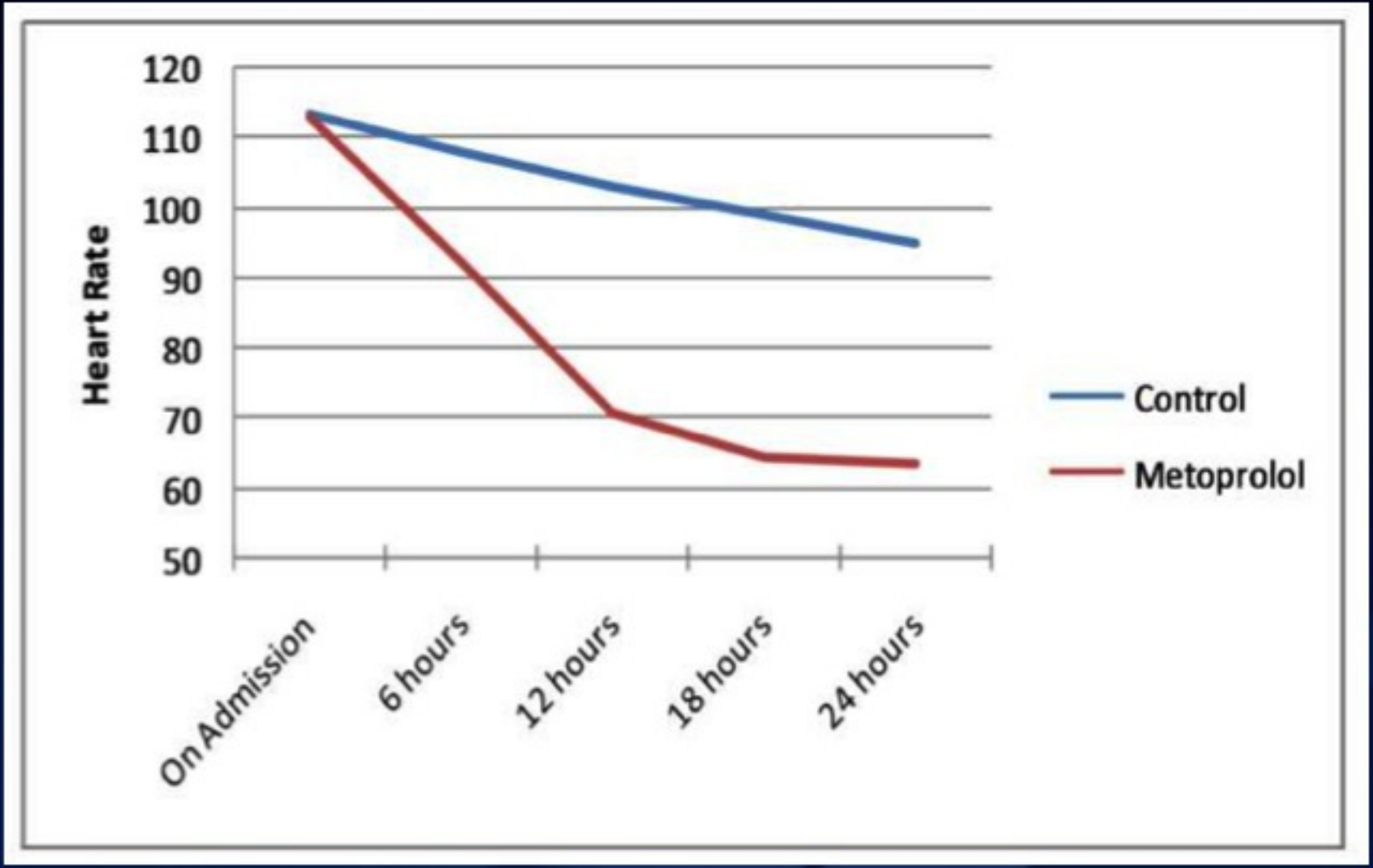
Beta-Blockers



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Beta-Blockers

Table (3): Absolute and relative risk reduction for mortality in different groups and subgroups.

Group	Absolute risk reduction	Relative risk reduction
Mortality in Metoprolol Vs. control	30%	47%
30 d-GOS (5) between Metoprolol and control (short- term mortality)	30%	60%
Mortality in early vs. late achievers	57.2%	86%
30 d-GOS (5) between early and late achievers (short- term mortality)	50.8%	91%
Mortality reduction between Metoprolol and control groups for patients above 40 years	53.4%	69.5%

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Background

- Most studies don't examine TYPE of BB
- Difference between drugs
  - Selective vs. non-selective
  - Lipophilic vs. nonlipophilic
  - Half life of drug
  - IV vs. PO

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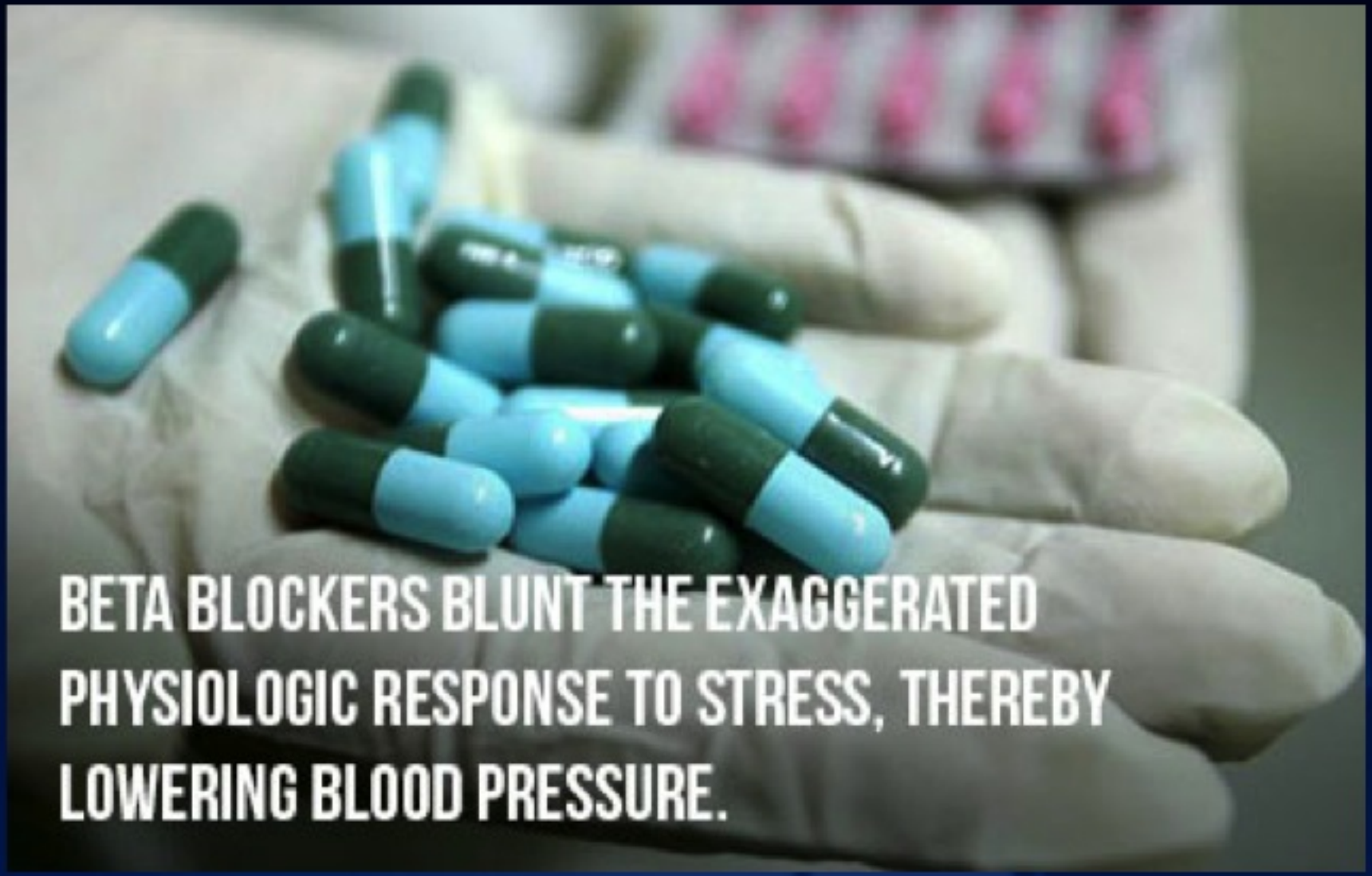

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Study Purpose

Examine differences between different beta-blockers and their effect on mortality

Methods

- Patients who received ≥1 dose of BB
- Registry merged with pharmacy data
- Variables examined
  - Demographics, Injury & clinical data
  - Type & doses of beta-blocker used

- Propensity Score matching

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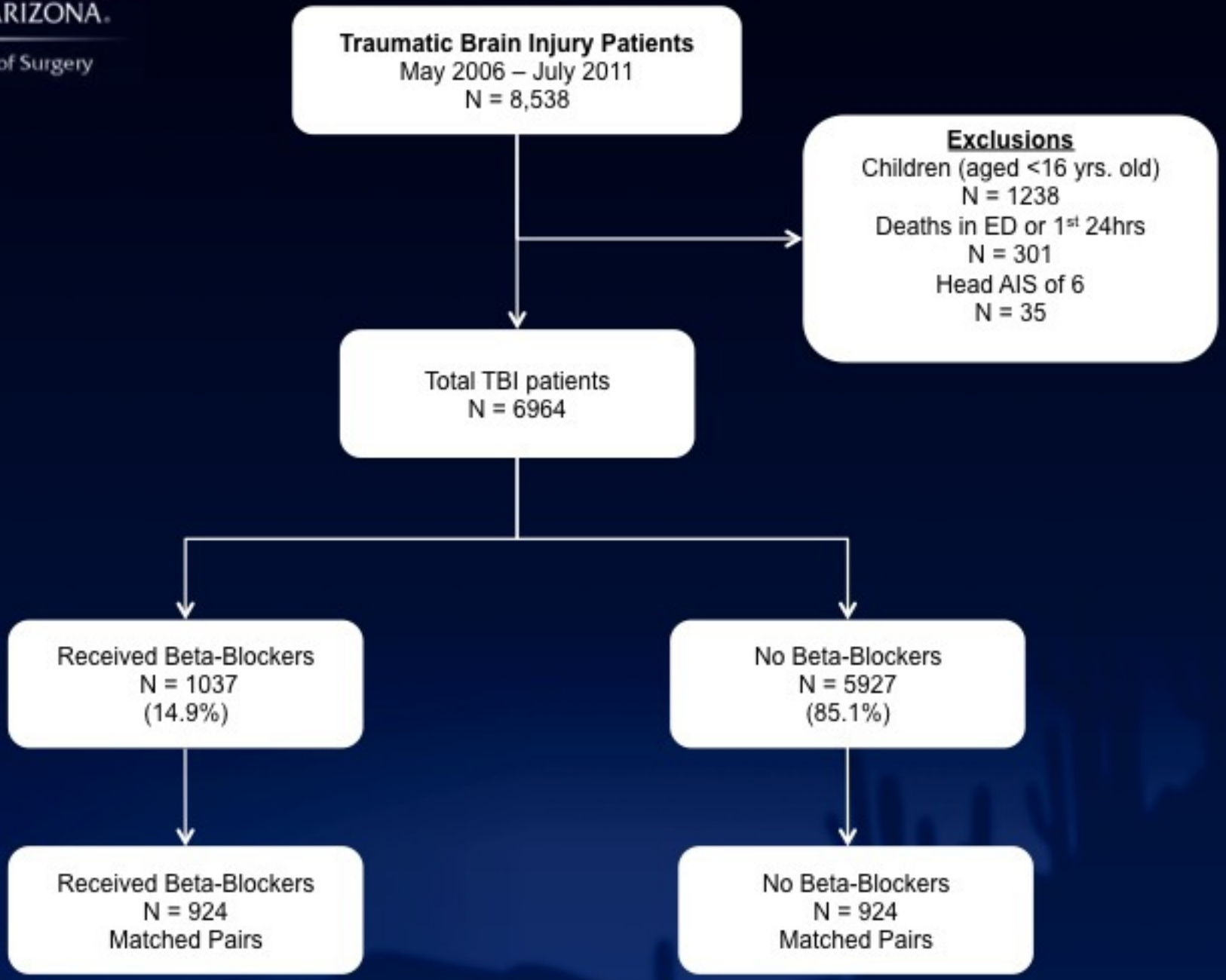
Figure 1. Study outline



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Demographics/Clinical Data

Variable	BB +ve N = 1037	BB –ve N = 5927	P Value
Age	57 ± 21	37 ± 18	<0.0001
Sex (% Male)	67.5%	66%	0.35
Race/Ethnicity Caucasian African-American Native American Asian	 88% 2% 4% 1%	 84% 3% 8% 1%	<0.0001 overall
ISS	21.3 ± 22.0	9.7 ± 10.0	<0.0001
Head AIS	3.3 ± 1.2	2.0 ± 1.1	<0.0001
RTS	7.5 ± 7.6	6.8 ± 6.9	<0.0001
Initial GCS	11 ± 5	14 ± 14	<0.0001
Intubated	45%	10%	<0.0001
Systolic BP in ED	149 ± 29	137 ± 22	< 0.0001

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Beta-Blocker comparison

- No survival advantage with BB
- Head AIS 1,2
  - 98.8% survival with BB
  - 99.8% survival without BB

P=0.005

- Head AIS 3,4,5
  - 87.4% survival with BB
  - 89.2% survival without BB

p = 0.19

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Propensity Matched Cohort

Variable	BB +ve N = 924	BB –ve N = 924	P Value
Age	55.9 ± 20.9	56.2 ± 19.9	0.68
Sex (% male)	67.3%	68.6%	0.55
Race/Ethnicity			0.83
Caucasian	87.3%	87.5%	
African-American	2.5%	2.5%	
Native American	4.1%	4.3%	
Asian	0.8%	0.5%	
ISS	20.4 ± 10.6	20.9 ± 12.9	0.43
RTS	6.8 ± 1.6	6.8 ± 1.6	0.99
Head AIS	3.3 ± 1.2	3.2 ±1.2	0.97
GCS	11.4 ± 4.9	11.4 ± 4.8	0.81
Intubated	41.2%	38.5%	0.23

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Propensity Matched Cohort

- Significant survival advantage with BB
- Head AIS 3,4,5
  - 88.7% survival with BB
  - 78.1% survival without BB p = 0.0001

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Propensity Matched Cohort

Outcome variable	BB +ve N = 924	BB –ve N = 924	P Value
Vent LOS	0 [0-80]	0 [0-30]	<0.0001
ICU LOS	3 [0-92]	1 [0-59]	<0.0001
Hospital LOS	7 [0-154]	2.5 [0-69]	<0.0001
Survival	91.5%	83.3%	<0.0001

Type of TBI

- No difference seen between groups
  - Epidural
  - Subdural
  - Subarachnoid
  - Skull fracture
  - Basal Skull fracture (25.2% vs. 21.2%, p=0.04)
  - Craniotomy
  - Craniectomy (1.2% vs. 0.1%, p=0.004)

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Propensity Matched Cohort

Beta-blocker	Paired N	Survival BB +ve	Survival BB -ve	P Value
Any Beta-blocker	924	91.5%	83.3%	<0.0001
Metoprolol	570	89.3%	80.0%	<0.0001
Propranolol	48	97.9%	75.0%	0.002
Labetalol	79	81.0%	83.5%	0.57
Atenolol	54	100%	100%	1.00
Carvedilol	40	95.0%	90.0%	0.32

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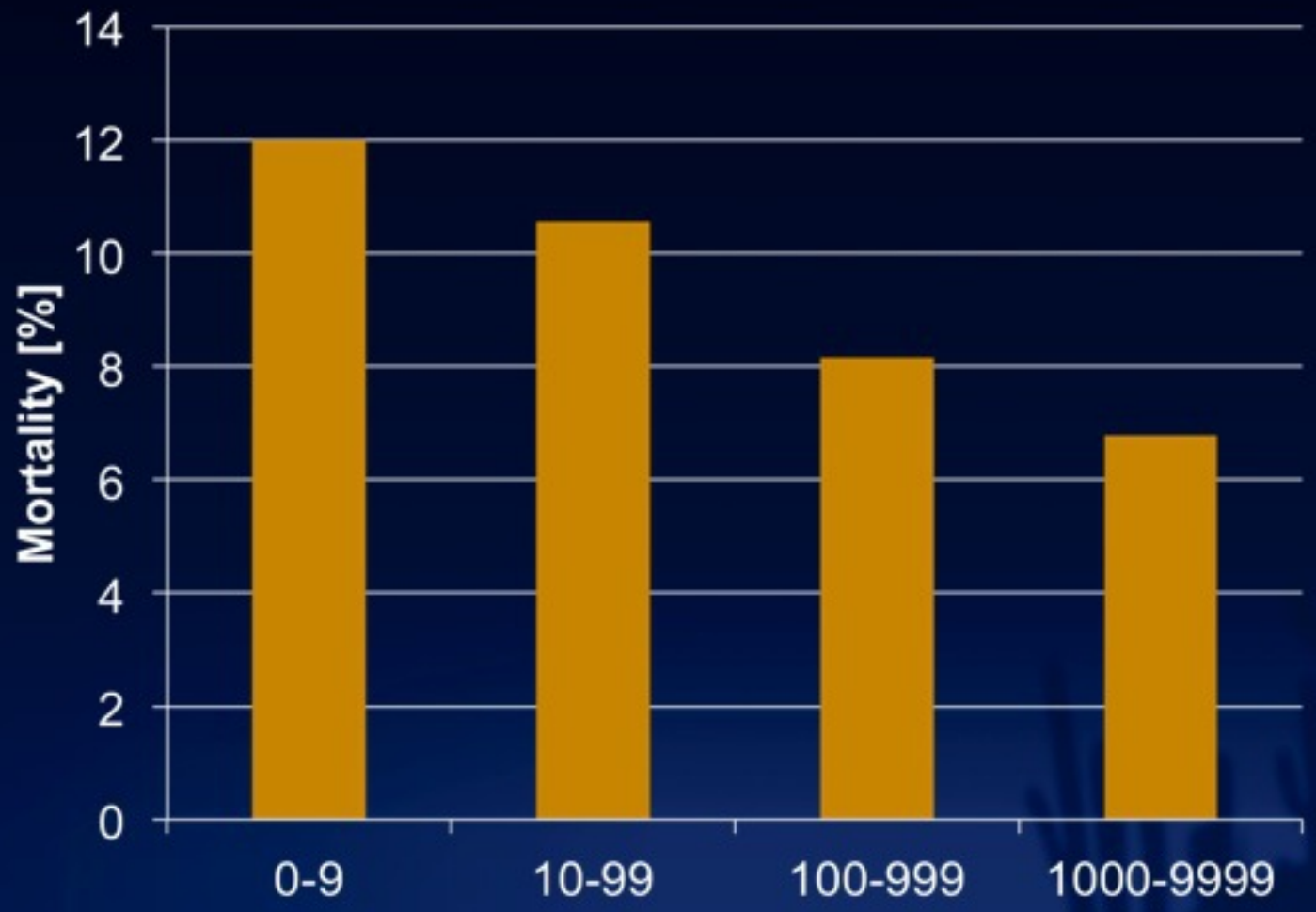
Dosing affects survival



Summary

- Association between BBs and survival
- Not significant in mild TBI
- NO improvement in length of stay
- Metoprolol and Propranolol most effective

Limitations

- Single Institution
- Propensity scoring only quasi-randomized
- Low numbers for BBs other than Metoprolol
- No information on heart rate

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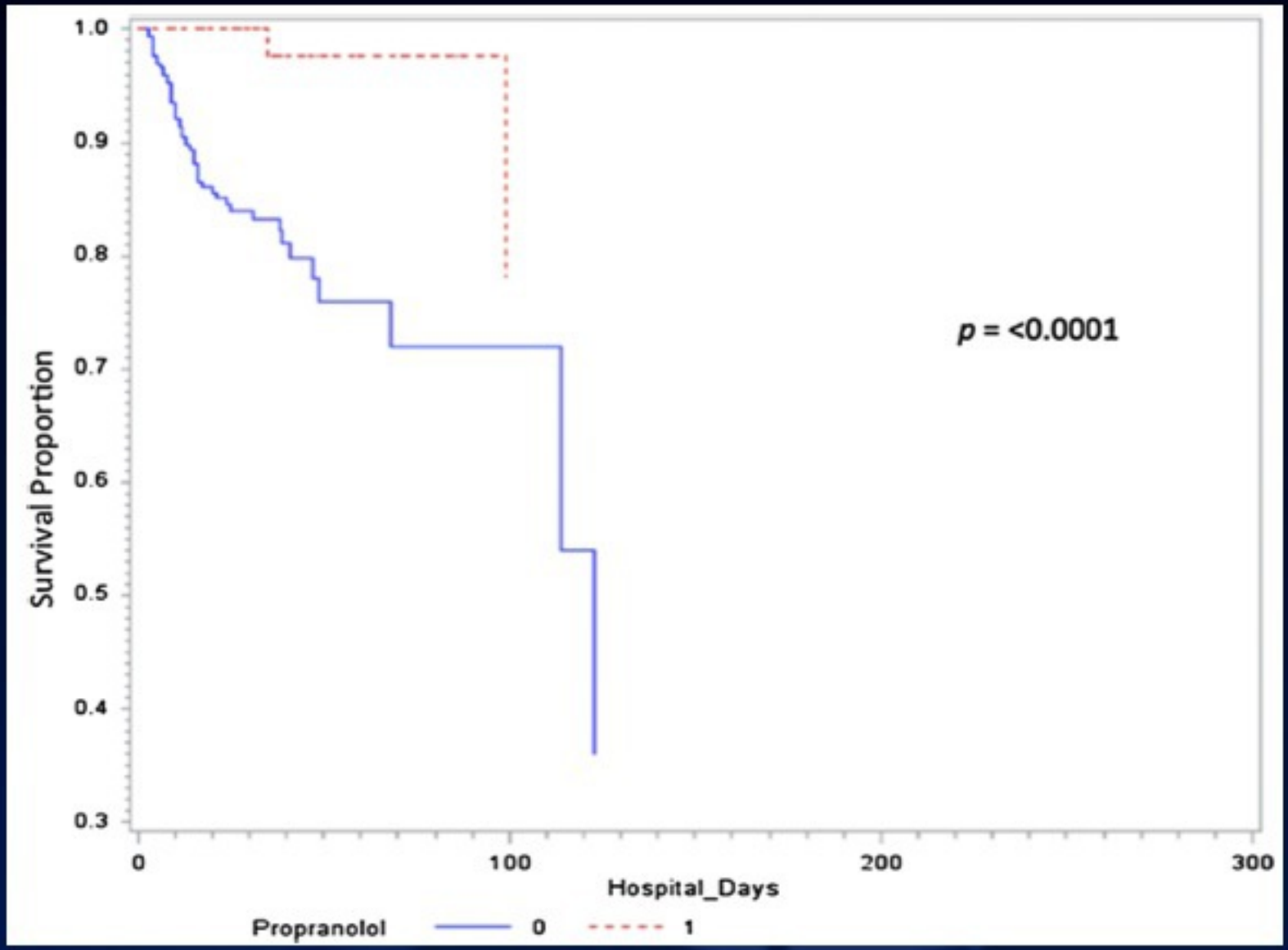
2014 research paper

- Schroeppel et al. - Memphis
- Compared Propranolol in pts with TBI

- 78 patients compared to 349


1.0
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Survival Proportion
p = <0.0001
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100
200
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Hospital_Days
Propranolol
0
1

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Conclusions

- Association of BB with improved survival
- Not all BBs have this effect

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TREATME… …MATIC BRAIN INJU…

in partnership with NETT Neurological Emergencies Treatment Trials

- Home
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- Fast Facts
- About Emergency Research
- Community Opinion Survey
- Opt-out Information
- Participating Sites
- NETT Network
- Investigator Tools (membership required)
- Articles
- Online Links
- Contact Us
- Treatment Guidelines

ProT… …ew

Proges… …he Treatment of Traumat… (ProTEC… …search study to see if … hormone … …our bodies, is … …e amount of bra… …two small studies in … …ter TBI, may result in less b… …dy will test these findings and determ… …ment is in adults with moderate to severe TBI.

PRESS RELEASE

Atlanta To Serve as National Epicenter for Promising Phase III Brain Injury Treatment Trial

The city of Atlanta will soon serve as the national epicenter for a groundbreaking National Institutes of Health (NIH)-sponsored Phase III trial for the treatment of traumatic brain injuries using the hormone progesterone.

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Estrogen

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Erythropoetin

"Effect of Erythropoietin and Transfusion Threshold on Neurological Recovery After Traumatic Brain Injury" Robertson et al, JAMA. 2014 Jul 2;312(1):36-47.

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Therapy for TBI

Is it all hopeless then?

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DASH After TBI Study: Decreasing Adrenergic or Sympathetic Hyperactivity After Traumatic Brain Injury

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2014 by Vanderbilt University

Sponsor:
Vanderbilt University

Collaborators:
Vanderbilt Institute for Clinical and Translational Research (CTSA)
Eastern Association for the Surgery of Trauma (EAST)

Information provided by (Responsible Party):
Mayur Patel, Vanderbilt University

ClinicalTrials.gov Identifier:
NCT01322048

First received: March 2, 2011
Last updated: June 3, 2014
Last verified: June 2014
History of Changes

Purpose

The investigators intend to determine the effect of adrenergic blockade on 1) short-term physiology, behavior, and cognition and 2) long-term neuro
Brain Injury (TBI).

The primary hypothesis is that adrenergic blockade after severe TBI will be associated with increased ventilator-free days.

Condition	Intervention
Brain Injuries Craniocerebral Trauma Trauma, Nervous System Traumatic Brain Injury	Drug: IV Propranolol and Per Tube Clonidine Drug: Placebo

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So, in or out?

- I say – IN

- AFTER Resuscitation
- HOLD parameters
- MORE doses are better than fewer
- ESPECIALLY in adrenergic storm