What are Appropriate End-points for Delirium Prevention/Treatment Studies

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Disclosure

- Salary support
  - Vanderbilt Physician Scientist Award (2003-2005)
  - Foundation of Anesthesia Education and Research (2005-2007)
  - VA Career Development Award (2008-2011)
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- Research grant from Hospira Inc

Unique Challenges in Delirium Research

- Delirium is a syndrome with multiple risk factors
- Lack of consensus of “what constitutes delirium”
- Fluctuating course- potential for missing delirium
- Some delirium may resolve on its own irrespective of therapy
- Drop out/attrition
  - Death, withdrawals, adverse events
    - Problem not just an issue of sample size but more importantly about validity of data given missing outcome data

Common Delirium Specific Outcomes

- Delirium incidence/prevalence
- Delirium Duration
- Time to event- first episode of delirium or resolution of delirium
- Delirium-free days
- Delirium/Coma-free days

Common End of Trial Outcomes

- Incidence/Prevalence of Delirium

Important from a patient perspective

Incidence/Prevalence or Duration of Delirium

- Limitations
  - True incidence/prevalence missed due to fluctuation in mental status
  - If fixed follow up period, delirium may be missed
  - Treatment may not have enough time to impact outcome
    - Issue in populations where the delirium is front loaded
    - E.g. critically ill patients and many post-op patients

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

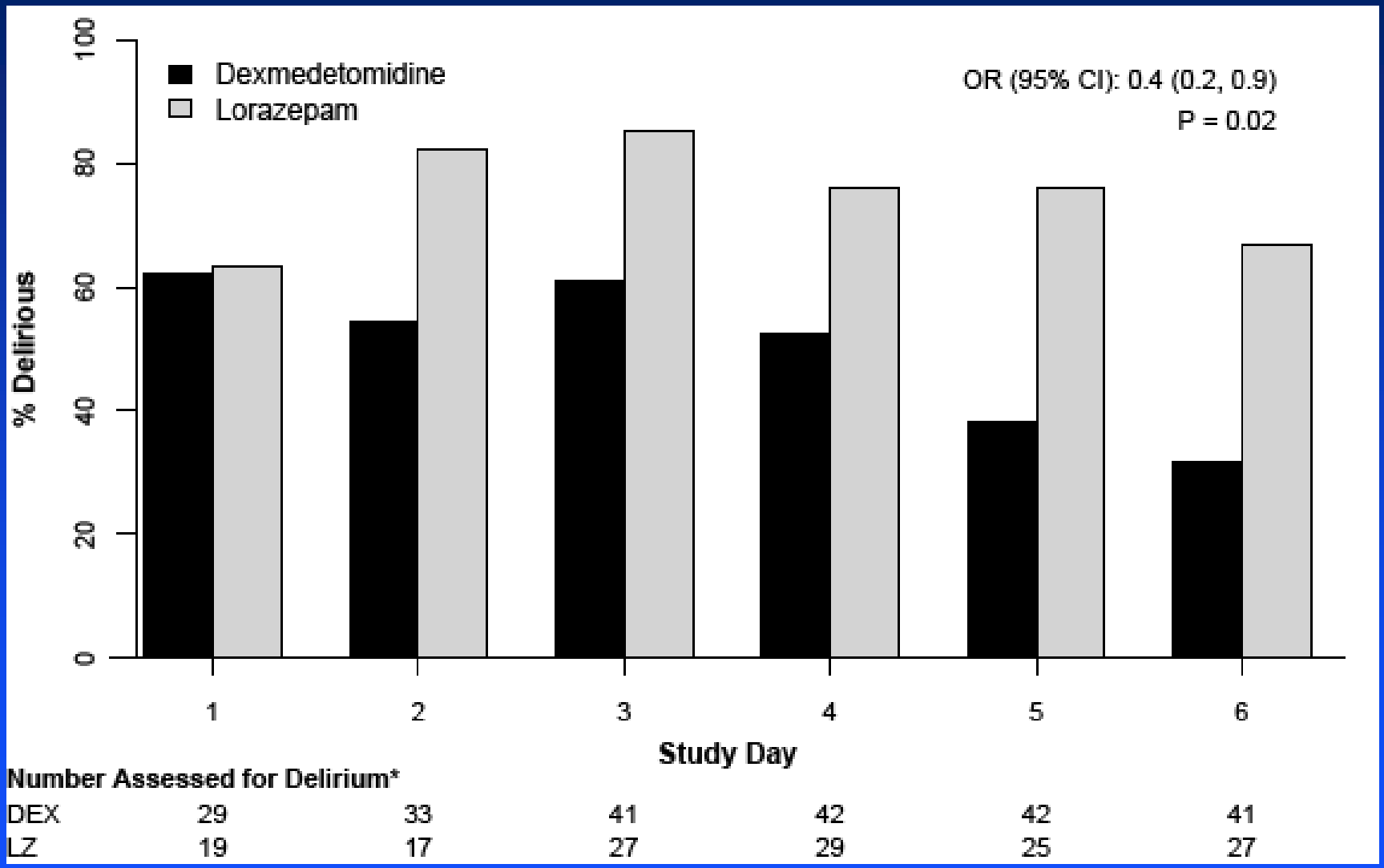
The MENDS Randomized Controlled Trial

Pratik P. Pandharipande, MD, MSCI

Context Lorazepam is currently recommended for sustained sedation of mechani-

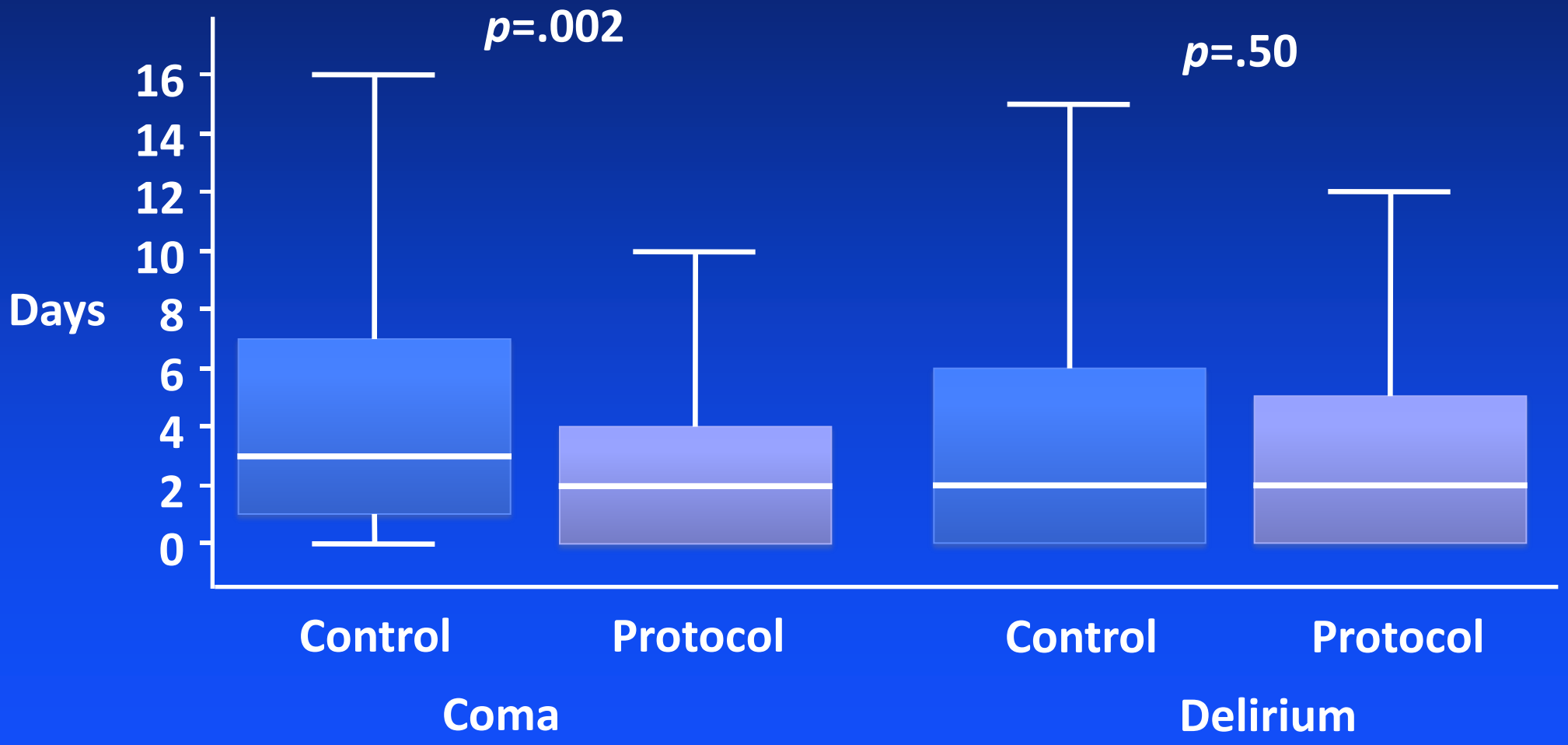
Prevalence of brain organ dysfunction, No. (%)[c]			
Delirium or coma	45 (87)	50 (98)	.03
Delirium	41 (79)	42 (82)	.65
Coma	33 (63)	47 (92)	<.001

Risk of Developing Delirium in MENDS



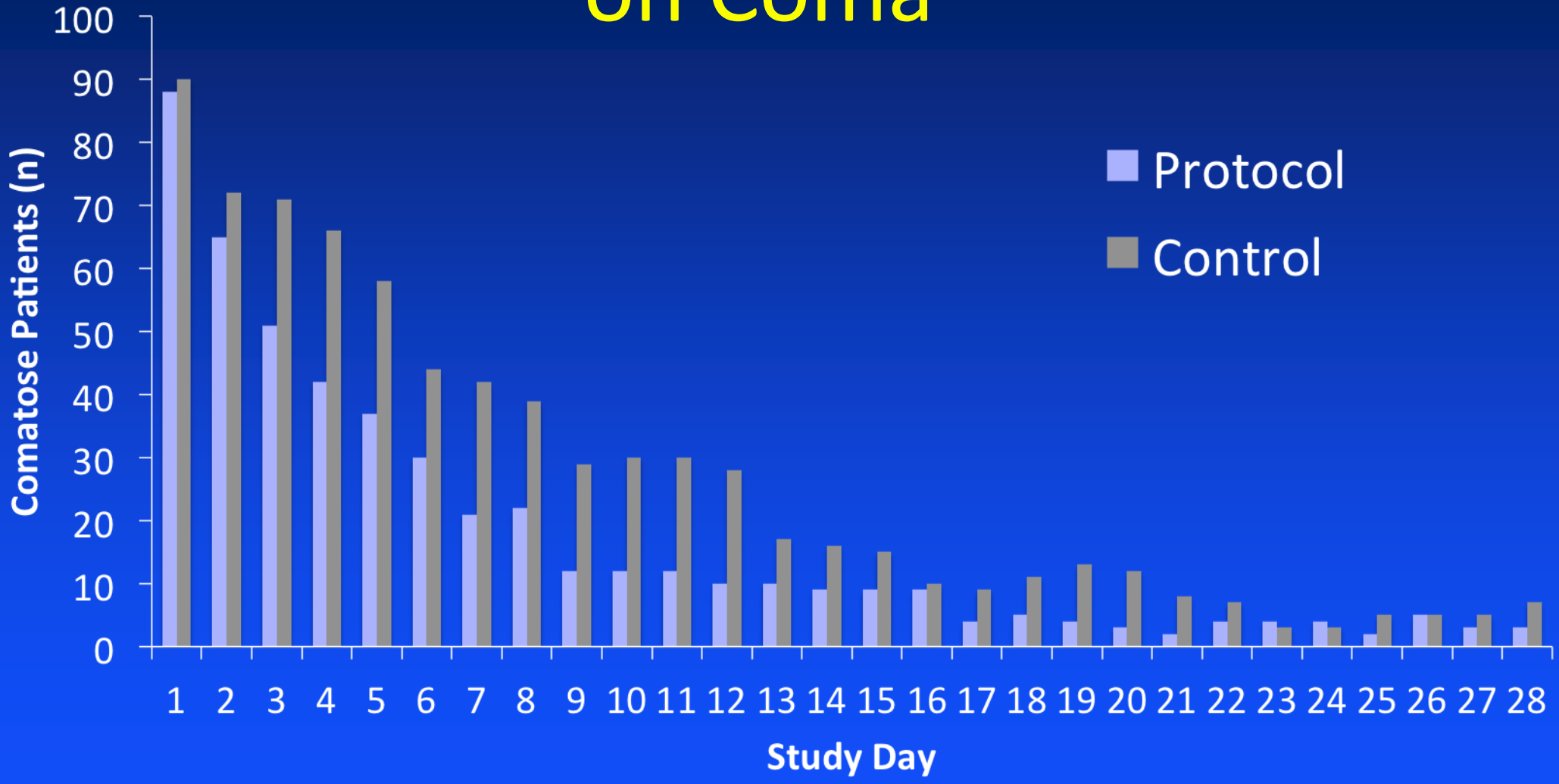
Pandharipande PP, et al. Critical Care. 2010, 14(2):R38)

Delirium Days



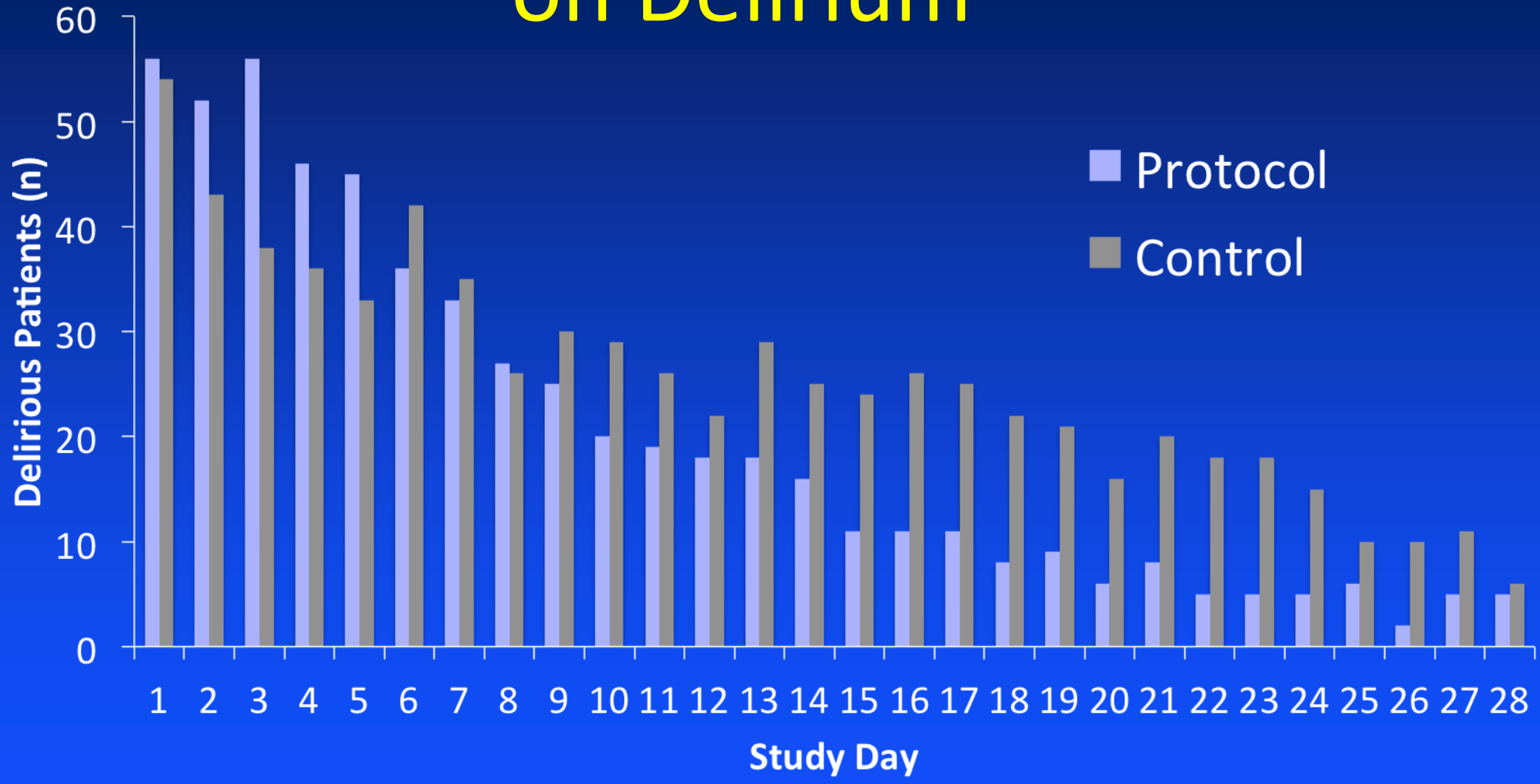
Girard TD, et al. Lancet 2008;371:126-34

Effect of Wake Up and Breathe on Coma



Girard TD, et al. Unpublished data from the ABC Trial.

Effect of Wake Up and Breathe on Delirium



Girard TD, et al. Unpublished data from the ABC Trial.

Time to Event Outcomes

- Time to first Episode of Delirium
- Time to Resolution of Delirium

May have some real world benefit if it translates into faster MV liberation or shorter LOS

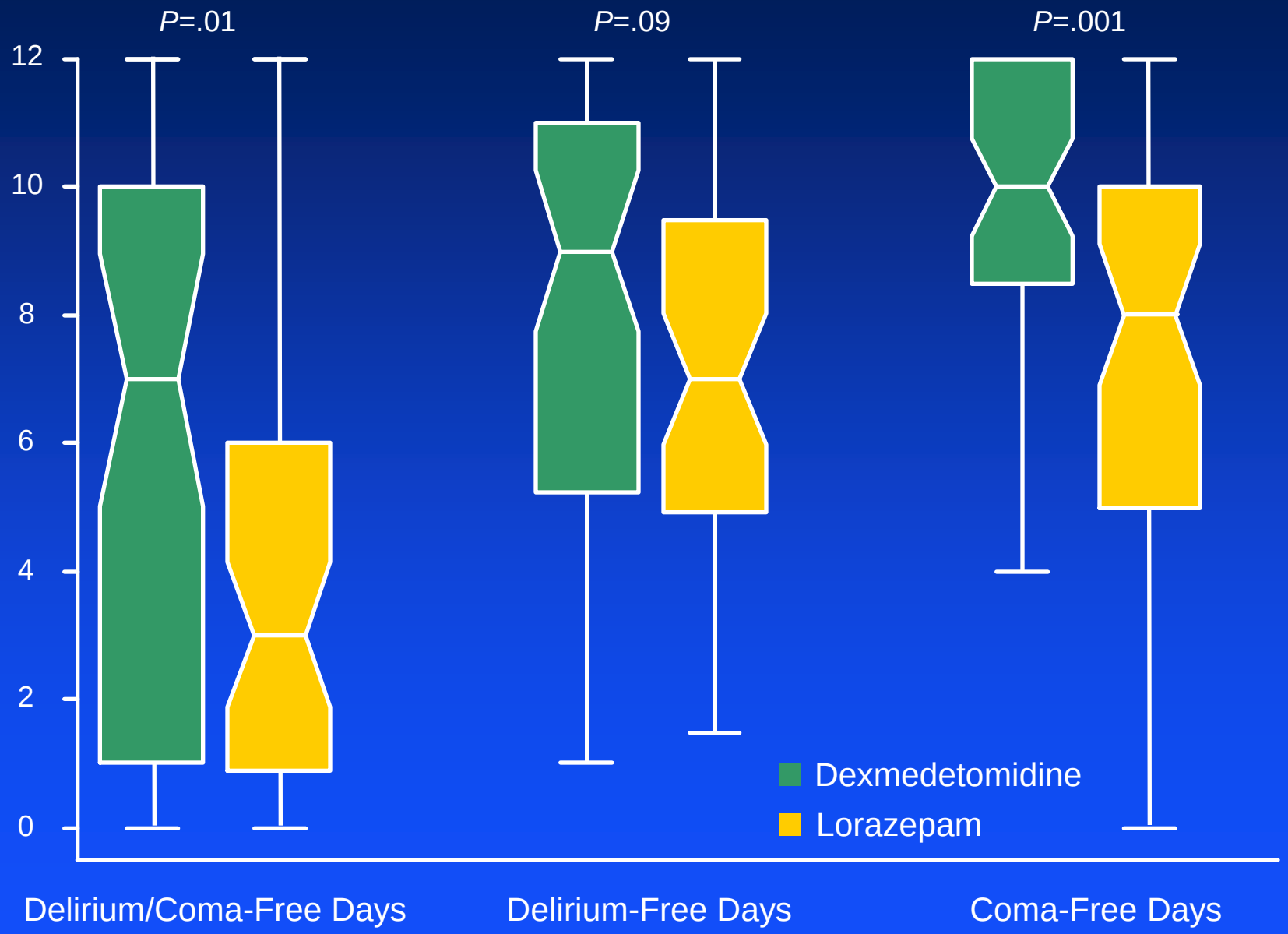
Time to Event Analysis

- Limitations
  - Does not allow recurrence of criterion event
    - What happens if you have resolution of delirium and then have delirium again
    - What constitutes resolution of delirium?
  - Addressing competing risks
    - Early time to first episode of delirium may be a better option than being in a coma and not eligible for delirium assessment

Event-free Outcomes

- Delirium-free days
- Delirium-coma free days
  - Attempt to account for confounding by death and coma

Event-free Outcomes



Pandharipande PP, et al. *JAMA.* 2007;298:2644-2653.

Mortality (Short or long-term)

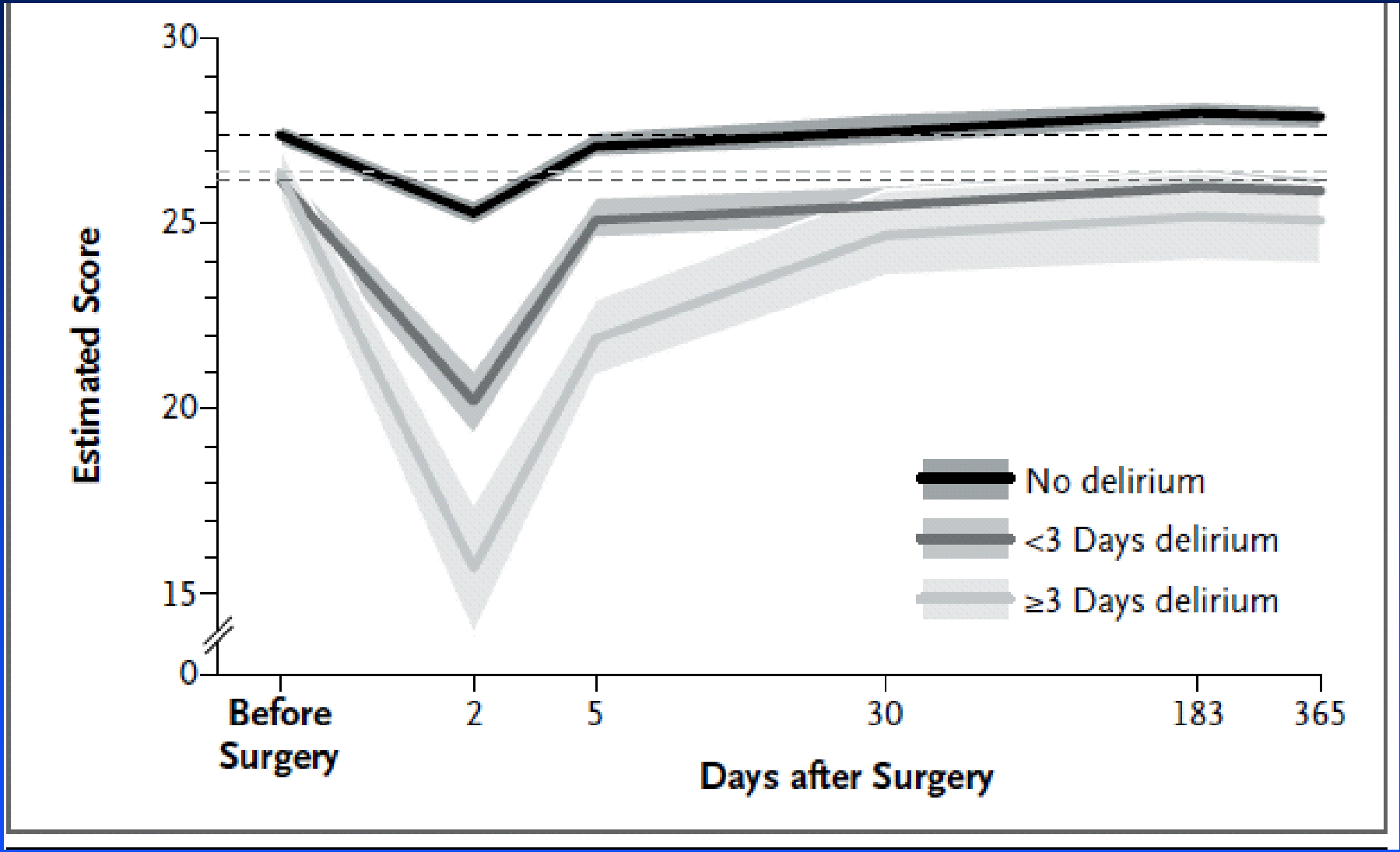
- While many prospective cohort studies have shown an association between delirium and mortality, no prevention/treatment trial of delirium has YET demonstrated any mortality benefit even when rates/duration of delirium were altered
  - Is this because “different delirium” have different mortality risks and we are not targeting the right type of delirium?
  - Is it because many patients do not consent/ or withdraw for interventional trials and those may have been the ones who were likely to have worse outcomes?

Daily Wake-Up + Early Mobility

Outcome	Intervention (n=49)	Control (n=50)	*P*
Functionally independent at discharge	29 (59%)	19 (35%)	.02
ICU delirium (days)	2.0 (0.0-6.0)	4.0 (2.0-7.0)	.03
Time in ICU with delirium (%)	33% (0-58)	57% (33-69)	.02
Hospital delirium (days)	2.0 (0.0-6.0)	4.0 (2.0-8.0)	.02
Hospital days with delirium (%)	28% (26)	41% (27)	.01
Barthel Index score at discharge	75 (7.5-95)	55 (0-85)	.05
ICU-acquired paresis at discharge	15 (31%)	27 (49%)	.09
Ventilator-free days	23.5 (7.4-25.6)	21.1 (0.0-23.8)	.05
Length of stay in ICU (days)	5.9 (4.5-13.2)	7.9 (6.1-12.9)	.08
Length of stay in hospital (days)	13.5 (8.0-23.1)	12.9 (8.9-19.8)	.93
Hospital mortality	9 (18%)	14 (25%)	.53

Schweickert WD, et al. *Lancet*. 2009;373:1874-1882.

Long-term Cognitive Impairment



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British Journal of Anaesthesia **110** (S1): i98–i105 (2013)
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BJA

Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

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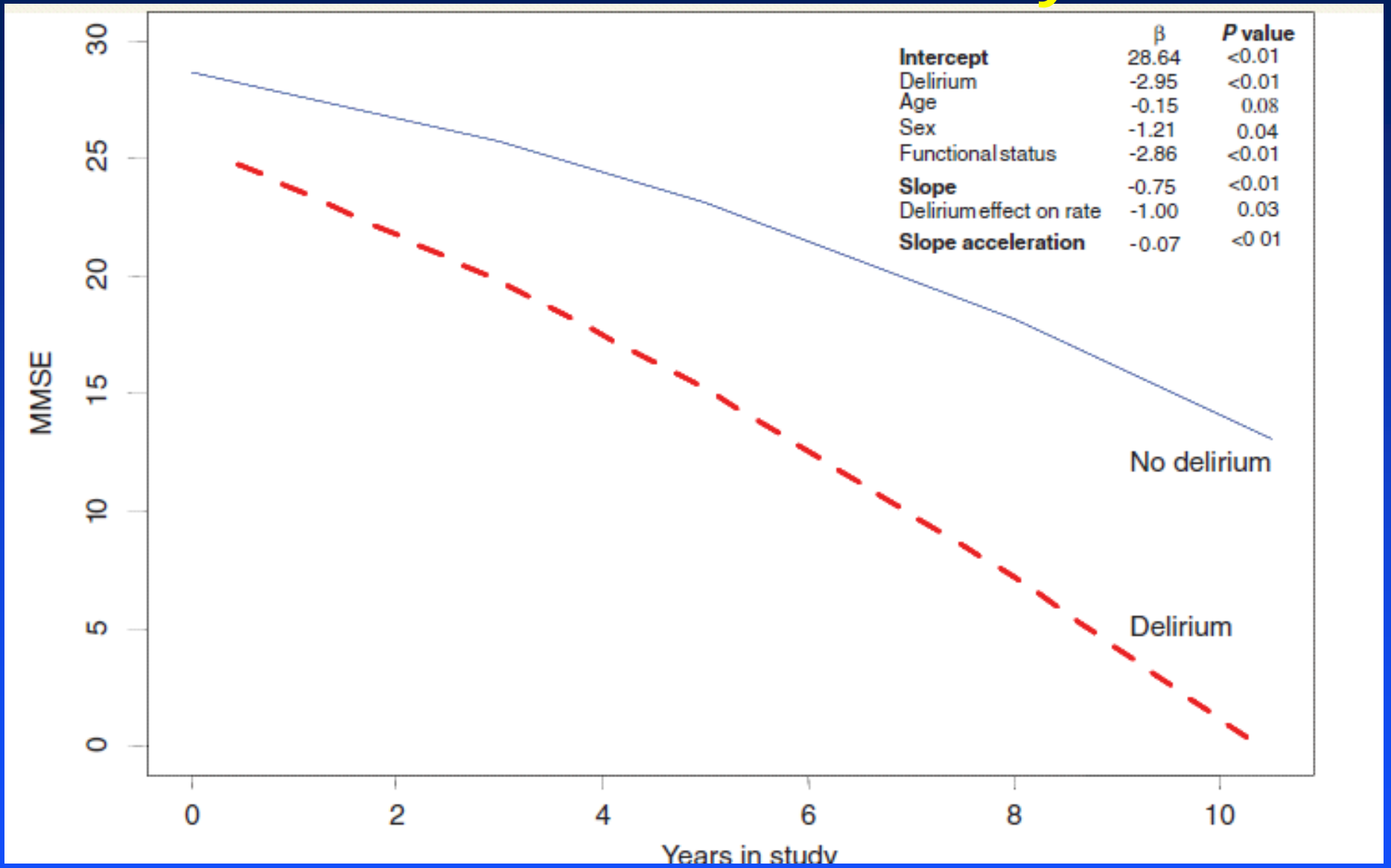
VANTAA 85+ Study

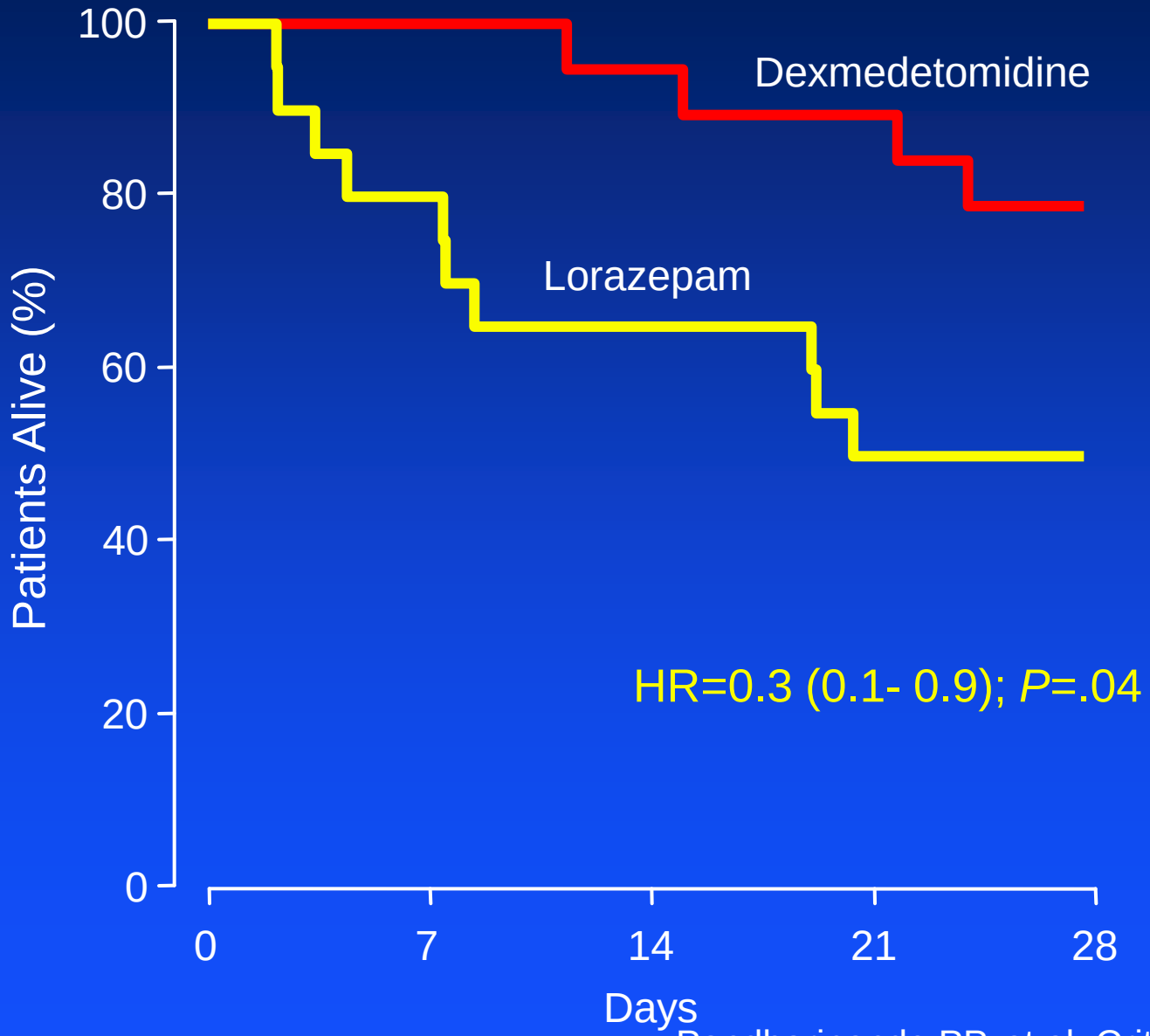


Davis D. Brain 2012; 135; 2809-16

Targeting Sub-groups for Mortality or LTCI outcomes

- Older patients
- Patients with mild cognitive impairment
- Patients with dementia or mental illnesses such as PTSD, depression
- Patients with frailty
- Patients who have higher severity of illness
  - E.g. sepsis

28-Day Survival, Sepsis Patients: MENDS



Pandharipande PP, et al. Critical Care. 2010, 14(2):R38)

Resource Utilization

- ICU and hospital lengths of stay
- Duration of mechanical ventilation
- Transfer to rehabilitation hospital
- Cost of care
- Care-giver burden
- Functional Outcomes
- Return to employment

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Multicomponent Targeted Intervention to Prevent Delirium in Hospitalized Older Patients

What is the Economic Value?

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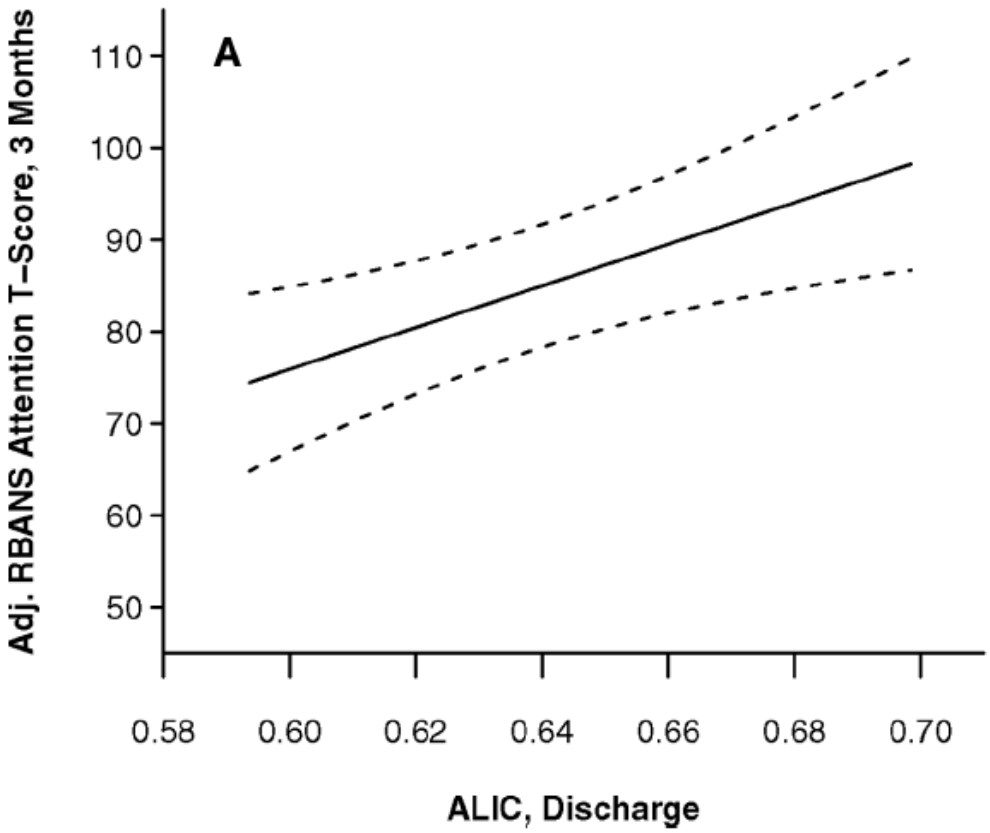
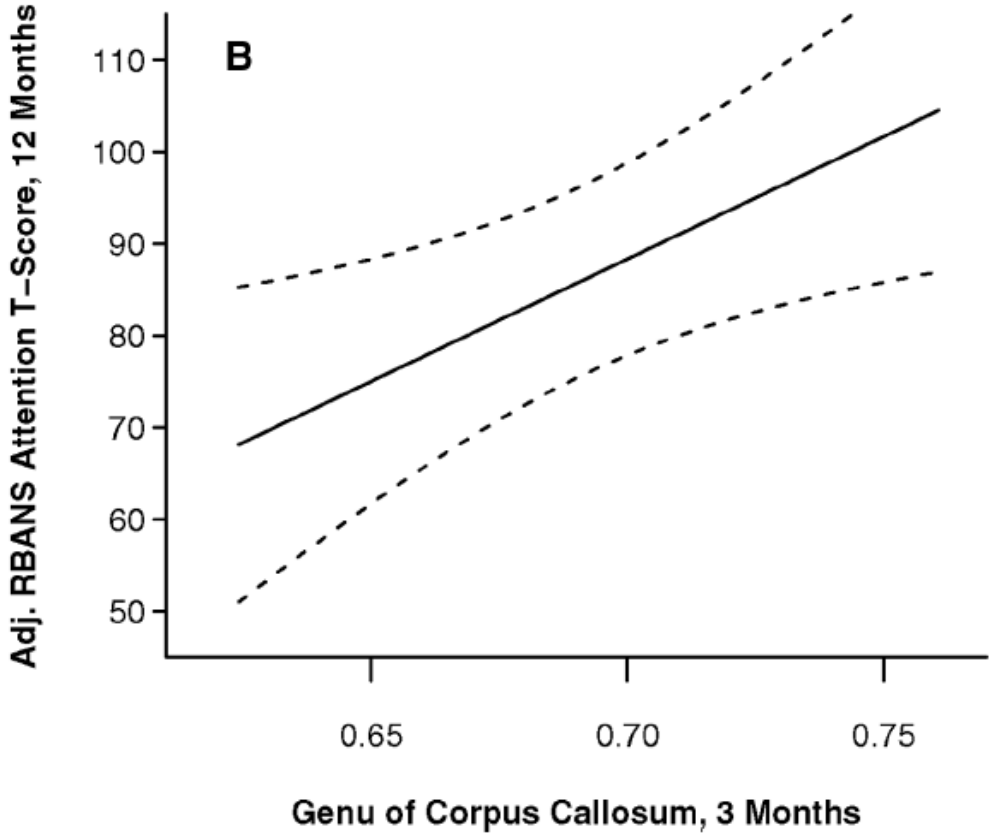
We conclude that, from the health care provider perspective, our multicomponent targeted delirium intervention is cost effective among patients at intermediate risk for delirium—a group substantially larger in size than low- and high-risk groups. We believe that these results provide

The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: The VISIONS prospective cohort magnetic resonance imaging study*

Alessandro Morandi, MD, MPH; Baxter P. Rogers, PhD; Max L. Gunther, PhD; Kristen Merkle, BA;





Biomarkers and Delirium

- Identification of biomarkers associated with delirium and outcomes
- Effect of therapies on biomarker profile
- Studying the mediation effect of these biomarkers on the outcome of interest (delirium duration etc.)

Statin Use and Risk of Delirium in the Critically Ill
Valerie J Page, Daniel Davis et al. AJRCCM 2014

Statin administration the previous evening was associated with the patient being assessed as free of delirium (OR = 2.28, (CI 1.01 to 5.13) $p < 0.05$) and with lower CRP ($\beta = -0.52$, $p < 0.01$) the following day. When the association between statin and being assessed as free of delirium was controlled for CRP, the effect size became non-significant (OR = 1.56, (CI 0.64 to 3.79) $p=0.32$).

Thank You!