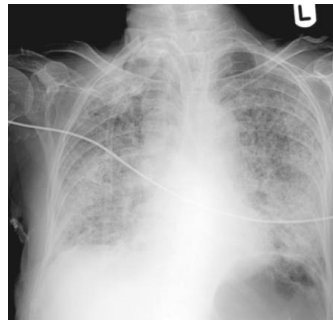


# Neuromuscular Blockade in ARDS



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# Disclosures

None

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Neuromuscular Blockers in Early Acute Respiratory  
Distress Syndrome

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for the ACURASYS Study Investigators\*

# Possible Mechanisms

## Lung mechanics

- Better synchrony
- More uniform recruitment
- Improved compliance
- Better gas exchange
- Better systemic oxygenation

## Lung inflammation

- Better control of insp V, P
- Less volutrauma
- Better control of exp V, P
- Less atelectrauma
- Less lung inflammation
- Less systemic inflammation

# Trade-offs



## Potential benefits

Synchrony  
Oxygenation  
Reduced VILI  
Survival

## Potential harms

Prolonged weakness  
Hemodynamics  
Cost

# Paralysis and Prolonged Weakness

## Overview

- case reports, case series, retrospective studies
- usually related to asthma, confounded by steroid use
- lacked objective, reliable measures
- lacked systematic screening

## Findings

- risk of prolonged weakness was related to dose, duration, and coexistent renal or hepatic dysfunction
- role of a class effect controversial
  - Aminosteroids (pancuronium, vecuronium, rocuronium) vs benzylisoquinolines (cisatracurium)

J. Garnacho-Montero

## **Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients**

- Prospective, controlled study (N = 73)
- All received electrophysiologic testing
  - Sensory and motor nerve conduction
  - Blinded assessments
- 14% received NMBA; 15% received steroids
- 50% developed critical illness polyneuropathy
- 18/73 survived; 8 had polyneuropathy (44%)
- OR 16.3 (1.3 – 199), p 0.0008
  - regardless of NMBA class
  - steroids not associated with weakness (NS)

# ICU physician survey 2002

Mehta S, Burry L, et al. Crit Care Med. 2006;34(2):374.

- Agents (across indications)
  - pancuronium, rocuronium, vecuronium
  - ...cisatracurium
- Monitoring
  - 61% physical exam
  - 84% PNS
- Daily interruption
  - 64% discontinued paralysis on a daily basis
- Protocols
  - 22% used a local protocol for neuromuscular blockade



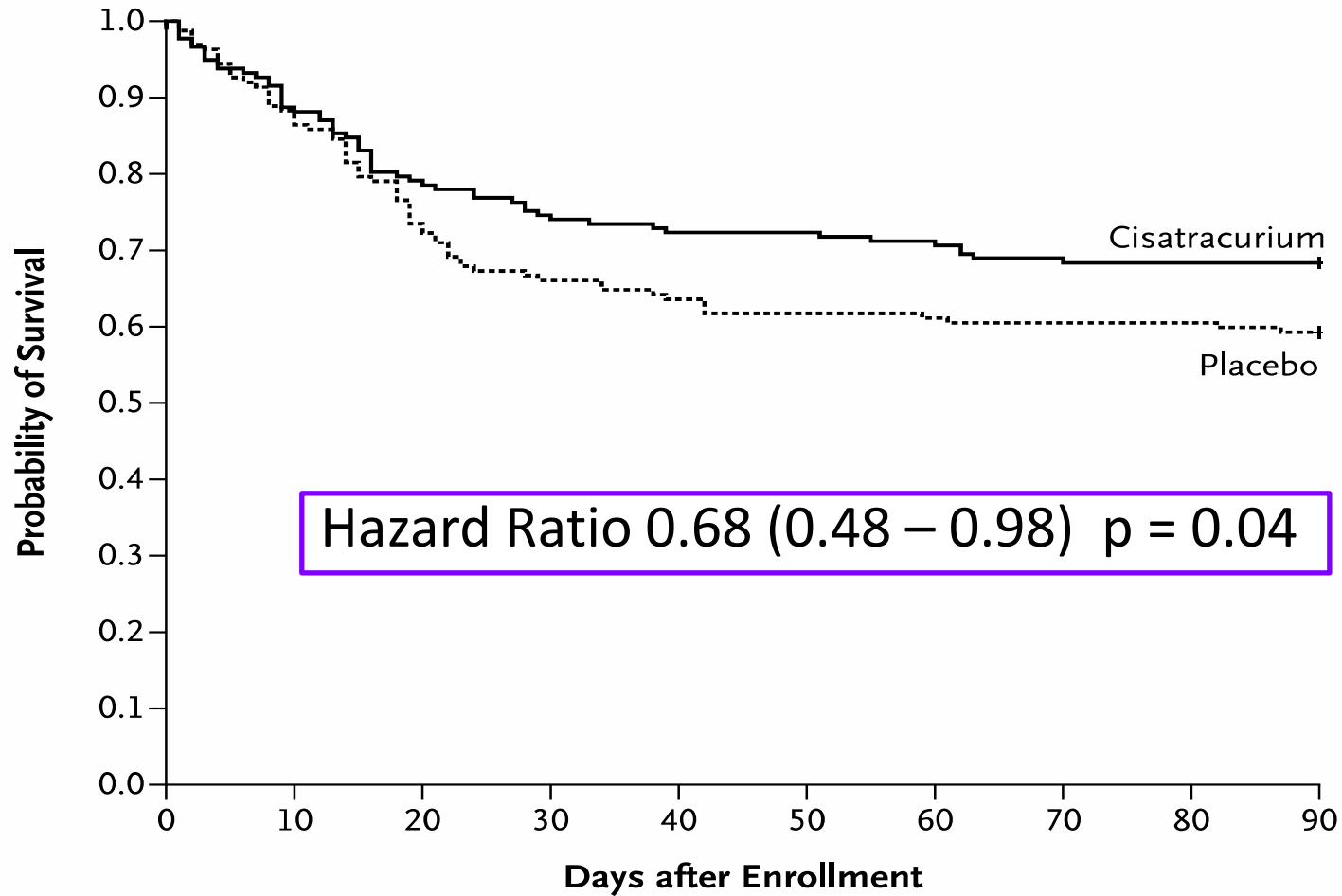
# Actual Use of NMBA

- ALVEOLI (P/F  $\leq$  300)... 25% ever, median 2 days
- EXPRESS (P/F  $\leq$  300)... 63% ever, median 3 days
- LOVS (P/F  $\leq$  250)... 44% ever, median 2.5 days
  
- OSCILLATE
  - (P/F  $\leq$  200)... 32.8% at baseline
  
- Randomized trials of low tidal volume ventilation
  - Burns, PLoS 2011
  - Compared to patients receiving traditional ventilation, significantly more patients managed with low Vt received paralysis
  - RR 1.37; 95% CI 1.04-1.82; p=0.03

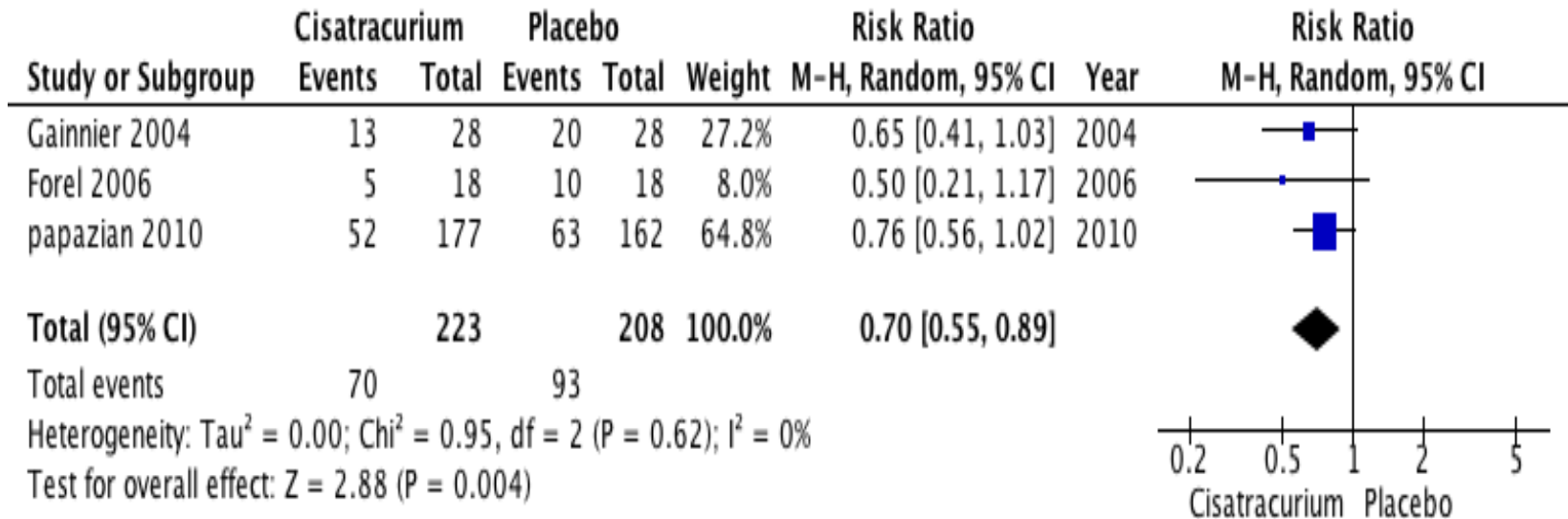
# ACURASYS

Design...	multicentre RCT
Patients...	340 patients with ARDS <ul style="list-style-type: none"><li>- early (&lt; 48h)</li><li>- severe (P/F &lt; 150)</li><li>- PEEP <math>\geq</math> 5 cm H<sub>2</sub>O; Vt 6-8 ml/kg</li></ul>
Paralysis...	cisatracurium infusion x 48 h
Control...	placebo infusion x 48 h
Both groups...	<ul style="list-style-type: none"><li>- deep sedation</li><li>- lung protective volume-AC</li><li>- 20 mg cisatracurium injection if Pplat &gt;32 cm H<sub>2</sub>O</li><li>- no peripheral nerve stimulation</li></ul>
Analysis...	adjusted RR hospital mortality at 90 days (P/F, SAPS II, Pplat)

# Mortality at 90 Days



# Meta-analysis: ICU Mortality



With permission, Dr. Waleed Alhazzani

**Table 3. Secondary Outcomes, According to Study Group.\***

Outcome	Cisatracurium (N = 177)	Placebo (N = 162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

# Context

Context of current care

Related trials

Criticisms of the trial

# Incomplete Blinding

- Adequate blinding of caregivers implausible for *some* patients, particularly those with profound respiratory acidosis and air hunger
- In general, unblinded studies overestimate treatment effects

**VALID CRITICISM; NOT A FATAL FLAW.**

# Lack of Monitoring

1. Depth of blockade
  - No peripheral nerve stimulation
  - Monitored Pplat
2. Ventilator dyssynchrony in the placebo group
  - Could inadequate monitoring and management of dyssynchrony in the placebo group predispose to worse outcomes?

**VALID CRITICISM; NOT A FATAL FLAW.**



# Suitability of MRC Scale

- Assessed strength in 3 muscles groups in each arm and leg, at 28 days or ICU discharge
- Recovery period may be too brief to detect differences, particularly if patients slow to awaken
- 10% of live patients did not contribute data
- Future approach
  - More protracted MRC assessments
  - Electrophysiologic assessments

**VALID CRITICISM; NOT A FATAL FLAW.**

# Summary

- many clinicians are already paralyzing in severe ARDS
- observational studies have rightly tempered our enthusiasm
- an imperfect but methodologically strong RCT suggests a survival benefit, at no apparent increased risk of prolonged weakness
- short-term neuromuscular blockade with cisatracurium for patients with severe ARDS (eg,  $\text{PaO}_2/\text{FiO}_2 \leq 120$ ) is probably safe and likely beneficial
- further study is required to replicate these findings

# Ideal NMB Agent

- rapid onset of paralysis
- titratable effect
- rapid offset, to allow neurologic assessments
- no adverse physiologic effects
- elimination independent of hepatic or renal function
- inactive metabolites
- modest cost

agent	onset (min)	duration (min)	renal – hepatic	active metabolit	adverse effects	cost
pancuronium	3-6	90	✓ ✓ ✓	✓ ✓	tachycardia	+
vecuronium	2-3	30-75	✓ ✓	✓ ✓		++
rocuronium	1.5-2	30-60	✓ ✓	✓	(tachycardia)	++
atracurium	2-3	30-60	(✓)		(CNS excitation) (hypotension)	+++
cisatracurium	2-3	45-60				++++

# Supportive Care

- **sedation** and analgesia prior to paralysis
- supervise closely - ventilator **disconnects** can be fatal
- **suction** based on amount of secretions – (no cough reflex)
- **elevate** head of the bed to reduce aspiration, and VAP
- artificial **tears**, tape eyelids to prevent corneal ulceration
- frequent **turning** and dry bedding to prevent skin breakdown
- enteral **feeding** is not contraindicated!

