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Learning Objectives

Upon completion of this program, participants will be able to:

- Define the most used sedation assessment scales in intensive care units (ICU) and explain their importance
- Summarize key pharmacokinetic/pharmacodynamic characteristics of sedative agents in the ICU
- Compare and contrast clinical use of various sedation agents in the ICU based on recent literature
- Design initiation and weaning-off sedation strategies for patients in the ICU

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Disclosures

- I have no real or apparent conflicts of interest to disclose
- I will not be discussing off-label or investigational uses of medications

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Post-Intubation Sedation

Mohammed Aldhaeefi, PharmD, BCCCP

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Post-Intubation

Medical Management

Physical Management

Patel SB. Am J Respir Crit Care Med. 2012;185(5):486-497

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Post-Intubation Period and Physical Management

- Securing the endotracheal tube
- Line suctioning
- Elevating the head of the bed

Patel SB. Am J Respir Crit Care Med. 2012;185(5):486-497

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Post-Intubation Period and Medical Management

- Pain management (analgesia-first)
- When pain is fully controlled, post-intubation sedation may be indicated:
  - Agitation
  - Relieve discomfort
  - Improve synchrony with mechanical ventilation
  - Decrease oxygen requirements
  - Decrease overall work of breathing
  - When paralytic use is indicated

Patel SB. Am J Respir Crit Care Med. 2012;185(5):486-497

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Pain Matters

- Mechanical ventilation for at least 24-hours
- No sedation vs. propofol/midazolam
- Bolus doses of morphine (2.5-5 mg) PRN

Outcome	No sedation	Sedation	p-value
Days without mechanical ventilation	13.8	9.6	**0.0191**
Length of stay	13.1	22.8	**0.0316**
Mortality	12	22	0.06

Strøm T. *Lancet*. 2010;375(9713):475-480

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NONSEDA Study

- Mechanical ventilation for at least 24-hours
- No sedation vs. light sedation (−2 to −3)
- Morphine for pain management
- Propofol was used for sedation in the first 48 hours and was replaced by midazolam thereafter

Olsen HT. *N Engl J Med*. 2020;382(12):1103-1111.

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NONSEDA Study

Significant Outcomes	Non-Significant Outcomes
Fewer patients without sedation had thromboembolic events	• Mortality • ICU length of stay • Ventilator-free days • Delirium/coma-free days

Olsen HT. *N Engl J Med*. 2020;382(12):1103-1111.

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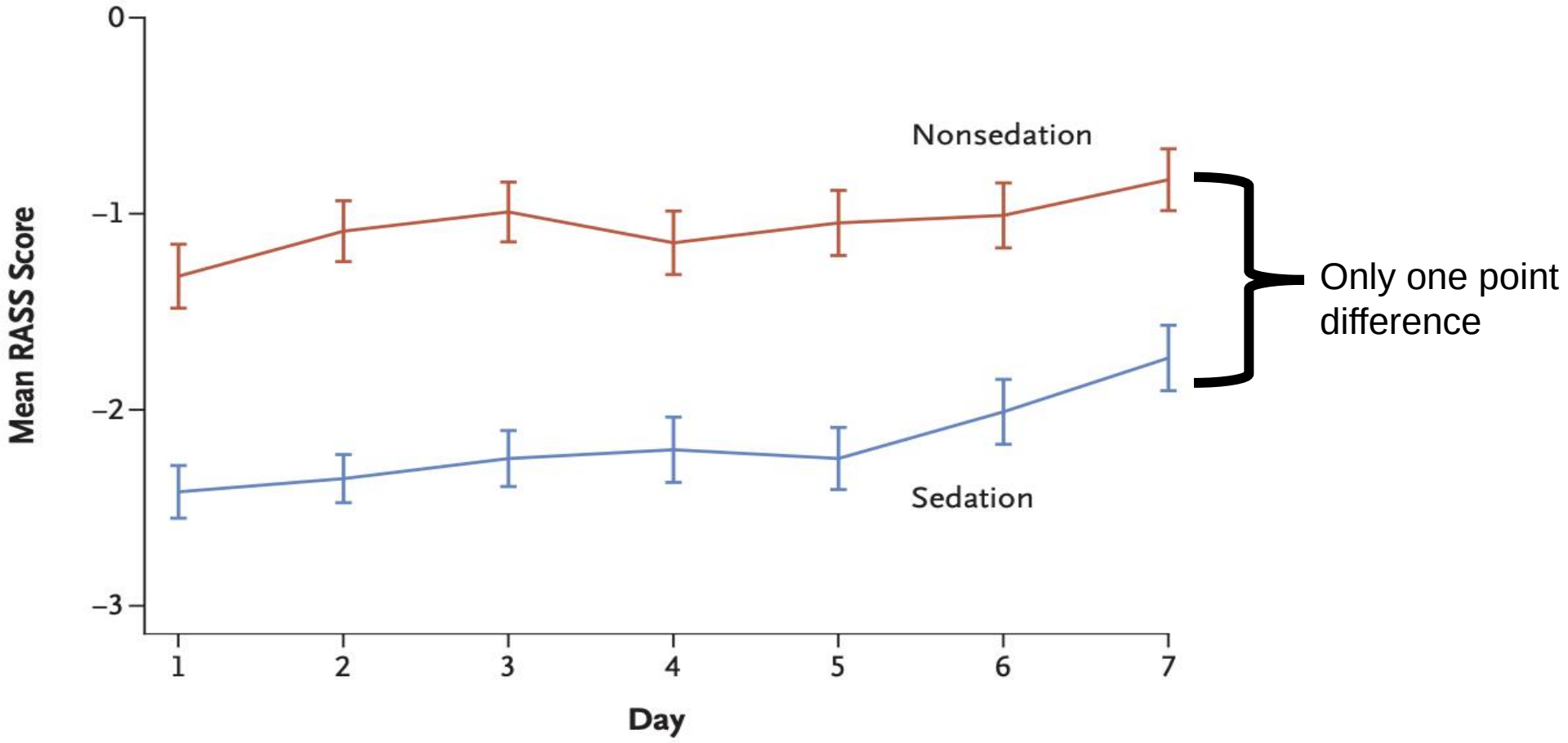
NONSEDA Study



Olsen HT. *N Engl J Med*. 2020;382(12):1103-1111.

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NONSEDA Study

- Average use of opioids was around 8 mg of morphine/day
  - Maybe more of opioids use reduction strategy?
- No 1:1 nursing assessment
- Not blinded
- No PTSD assessment

Olsen HT. *N Engl J Med*. 2020;382(12):1103-1111.

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Post-Intubation Period and Medical Management

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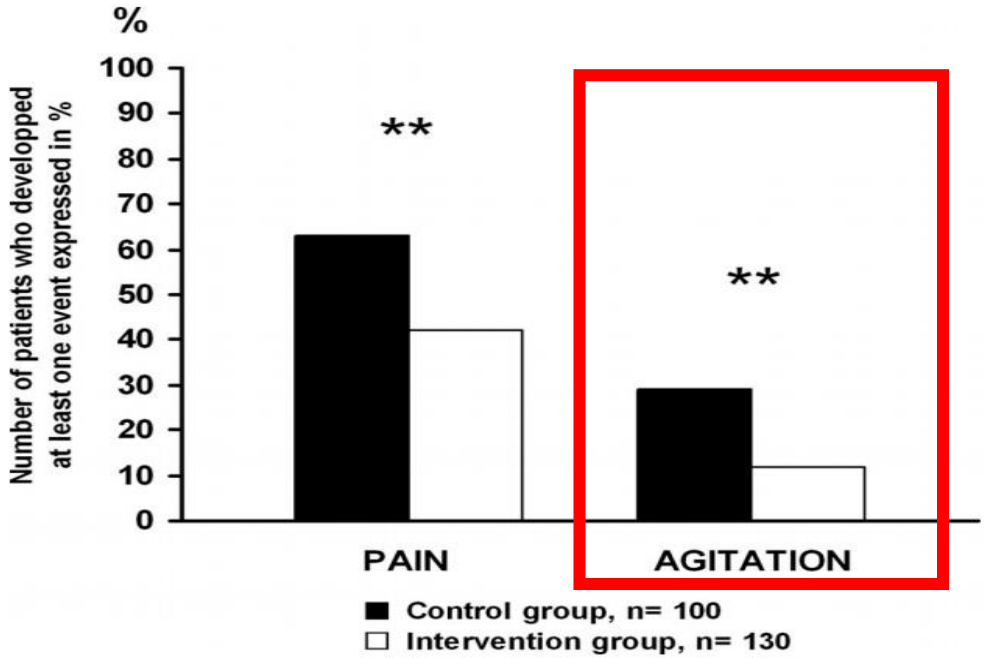
Why Do We Use Sedation in The ICU?

- Using RASS based assessment and sedation use resulted in reduction in duration of mechanical ventilation



Chanques G et al. *Crit Care Med* 2006. 34 (6) 1-9

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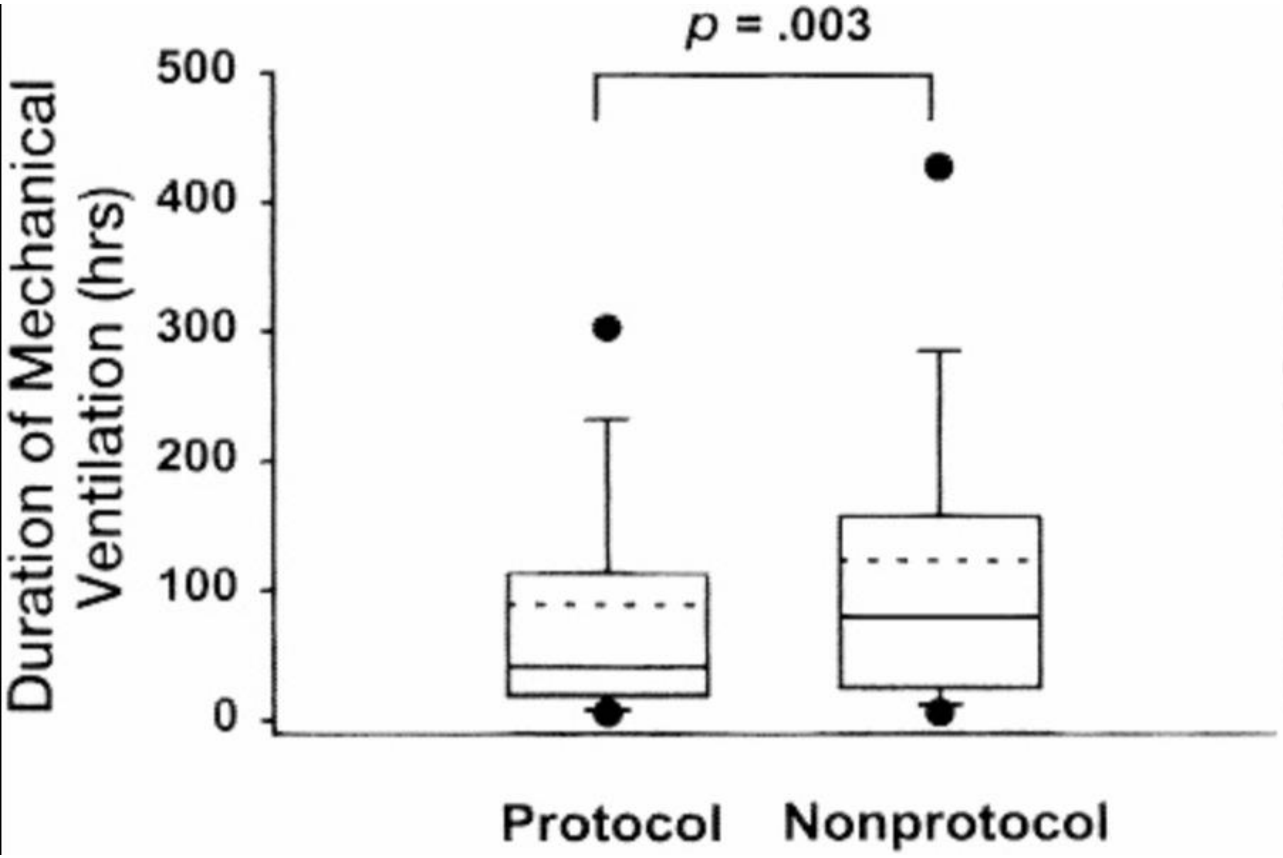
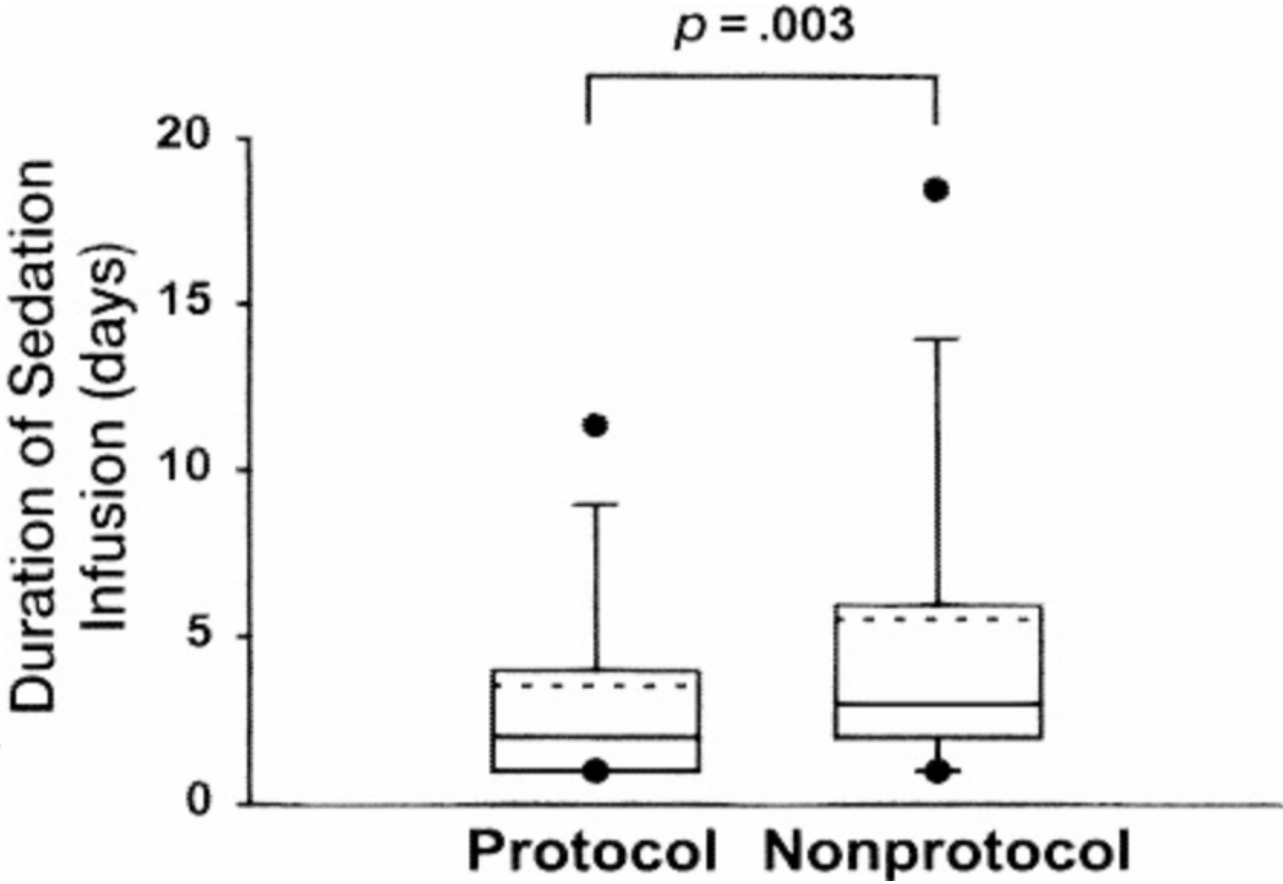
Why Do We Use Sedation in The ICU?





Nurse driven protocol resulted with lower duration of sedation use and lower duration of mechanical ventilation

Brook AD. *Crit Care Med*. 1999;27(12):2609-2615

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How to Assess Sedation in the ICU?

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Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Sessler CN. Am J Respir Crit Care Med. 2002;166(10):1338-1344.

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Riker Sedation-Agitation Scale (SAS)

• 7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side
• 6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
• 5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
• 4	Calm and cooperative	Calm, awakens easily, follows commands
• 3	Sedated	Difficult to arouse; awakens to verbal stimuli or gentle shaking, but drifts off again; follows simple commands
• 2	Very sedated	Arouses to physical stimuli, but does not communicate or follow commands, may move spontaneously
• 1	Unable to rouse	Minimal or no response to noxious stimuli, does not communicate or follow commands

Khan BA. *Chest*. 2012;142(1):48-54.

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RASS vs. SAS

- Excellent reliability with both
- CAM-ICU based on RASS
- Presence and sustainability cognition or comprehension only with RASS
- Mechanical ventilation synchrony only with RASS
- RASS provide distinction despite the single scale design (- vs +)

Sessler CN. *Critical Care*. 2008;12(Suppl 3):S2

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Bispectral Index (BIS)

- Measures the electrical activity in the brain
- Range:
  - 0 = COMPLETE absence of brain activity
  - 100 = FULLY awake
- Values between 40 - 60 represent adequate general anesthesia and showed “very low levels of post-operation recall”
- Values less than 40 represent a deep hypnotic state
- <20 = burst suppression

Ball J. Minerva Anestesiol. 2002;68(4):248-251
Bennett C. Anesth Analg. 2009;109(2):539-550

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BIS in The ICU

- **PADIS guidelines:** "BIS monitoring…during deep sedation or neuromuscular blockade"
- Low BIS associated with increasing delirium
  - Morbidity and mortality?
- Possible faster wakening times
- Currently no high-level evidence to guide use in ICU

Ball J. Minerva Anestesiol. 2002;68(4):248-251
Bennett C. Anesth Analg. 2009;109(2):539-550
Devlin J, et al. Crit Care Med. 2018

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Sedation Agents and Strategies

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Commonly Used Sedative Agents

- Propofol
- Dexmedetomidine
- Ketamine
- Benzodiazepines

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Sedative Agents

	MoA	Onset	Duration	Precautions	AE	PK	Dose
Propofol	$GABA_A$ Na channel Reduction of glutamate release	1 minute	Single bolus dose: 5-6 minutes Short term use: 0.5-1 hours Long term use: 25-50 hours	Hypotension, bradycardia, hepatic/ renal failure, pancreatitis	Respiratory depression, hypotension, bradycardia, PRIS	Hepatic conjugation, 2B6 CYP substrate	5–50 mcg/kg/min
Dexmedetomidine	Alpha adrenergic agonist	20-30 minutes	1-2 hours	Hepatic failure, bradycardia	Hypotension, bradycardia	Hepatic by glucuronidation and renal excretion, 2A6 CYP substrate	0.2–0.75 mcg/kg/hr

MoA: Mechanism of action
AE: Adverse effects
PK: Pharmacokinetics

Devlin J, et al. Crit Care Med. 2018
Reade MC. N Engl J Med. 2014;370(5):444-454
Hughes CG. Clin Pharmacol. 2012;4:53-63

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Sedative Agents

	MoA	Onset	Duration	Precautions	AE	PK	Dose
Benzodiazepines	$GABA_A$	3-10 minutes	2-8 hours	Delirium Midazolam: Hepatic failure Lorazepam: Renal failure	Metabolic acidosis, propylene glycol toxicity (lorazepam)	Lorazepam: hepatic conjugation Midazolam: phase I hepatic to alpha hydroxymidazolam, 3A4	Lorazepam bolus dose: 1–4 mg IV every 4–6 hours Midazolam: 1-5 mg/hour
Ketamine	NMDAR antagonist	0.5-1 minute	15 minutes	Dissociative anesthesia (2Cs + 2As)	Breathing difficulties, laryngospasm, increases salivary secretions	Hepatic N-demethylation by 3A4 to norketamine	1-2 mcg/kg/hour

AE: Adverse effects
PK: Pharmacokinetics; MoA: Mechanism of action

Devlin J, et al. Crit Care Med. 2018
Reade MC. N Engl J Med. 2014;370(5):444-454
Hughes CG. Clin Pharmacol. 2012;4:53-63

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2018 PADIS Recommendations

- "We suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults"

- "We suggest using propofol or dexmedetomidine over benzodiazepines (midazolam or lorazepam) for sedation in critically ill mechanically ventilated patients"

- "We suggest using propofol over benzodiazepines (midazolam or lorazepam) for sedation in mechanically ventilated patients after cardiac surgery"

Devlin J, et al. Crit Care Med. 2018

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Devlin J, et al. Crit Care Med. 2018

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Light vs. Deep Sedation/MENDS2 and Sepsis Patients

- Dexmedetomidine (0.2-1.5 mcg/kg/hr) vs propofol (5-50 mcg/kg/min)
- No difference between dexmedetomidine and propofol in the number of days alive without delirium or coma (OR 0.96; 95% CI, 0.74 to 1.26)
- Ventilator-free days (OR 0.98; 95% CI, 0.63 to 1.51)
- Death at 90 days (38% vs. 39%; hazard ratio, 1.06; 95% CI, 0.74 to 1.52)

Hughes. N Engl J Med. 2021;384(15):1424-1436

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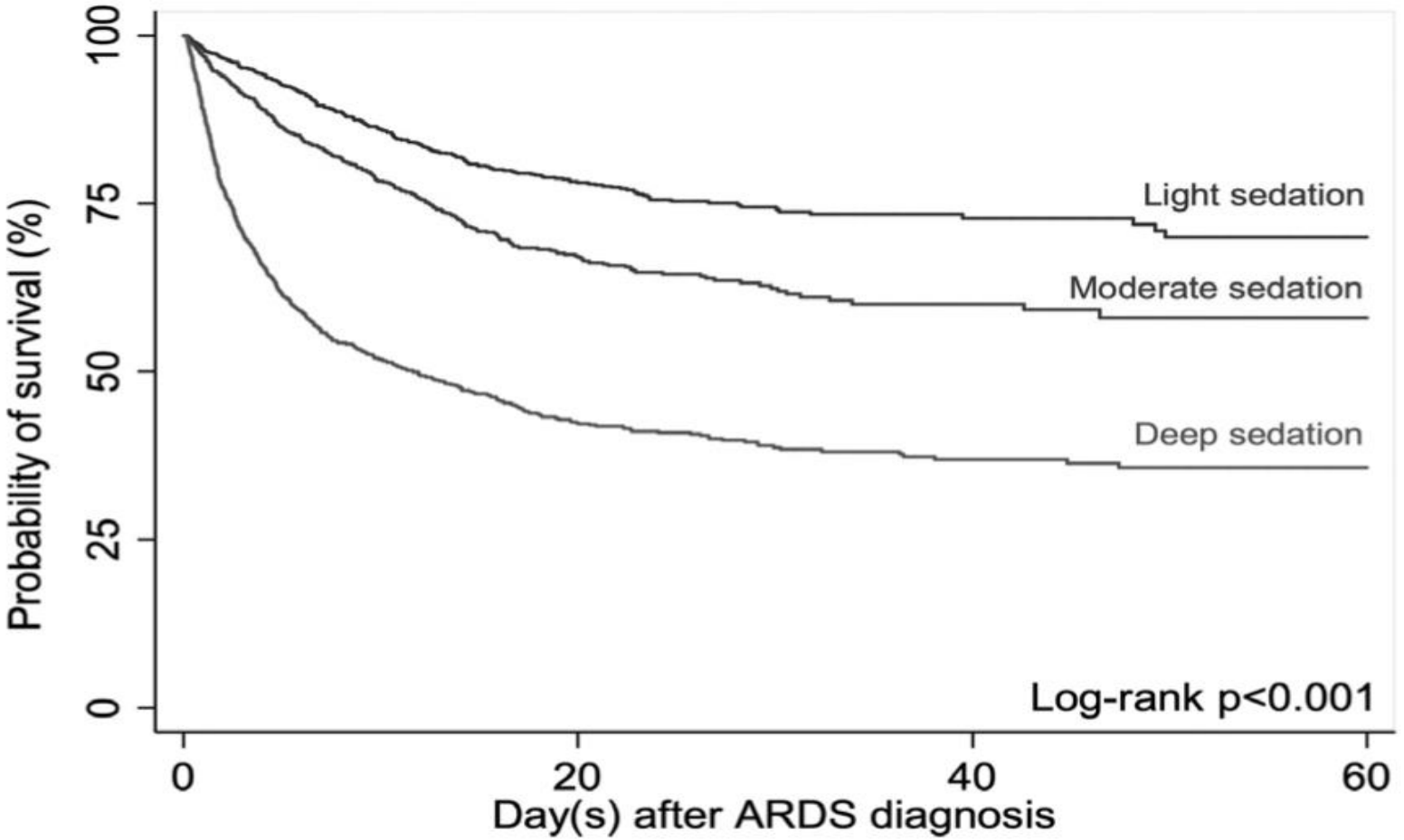
Light vs. Deep Sedation



Wongtangman K. *Critical Care Medicine*. 2021;Publish Ahead of Print.

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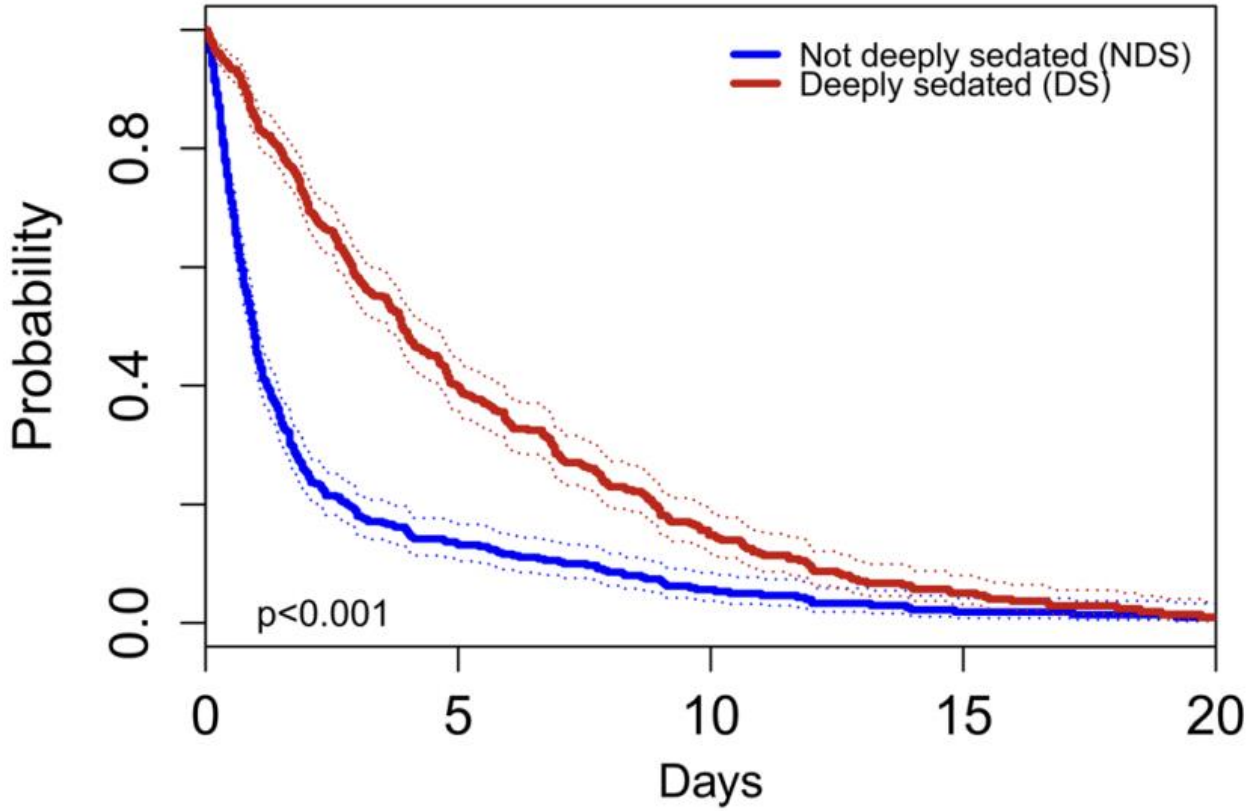
Light vs. Deep Sedation



Time to extubation 21 vs 76 hours

Balzer F. *Crit Care*. 2015;19:197

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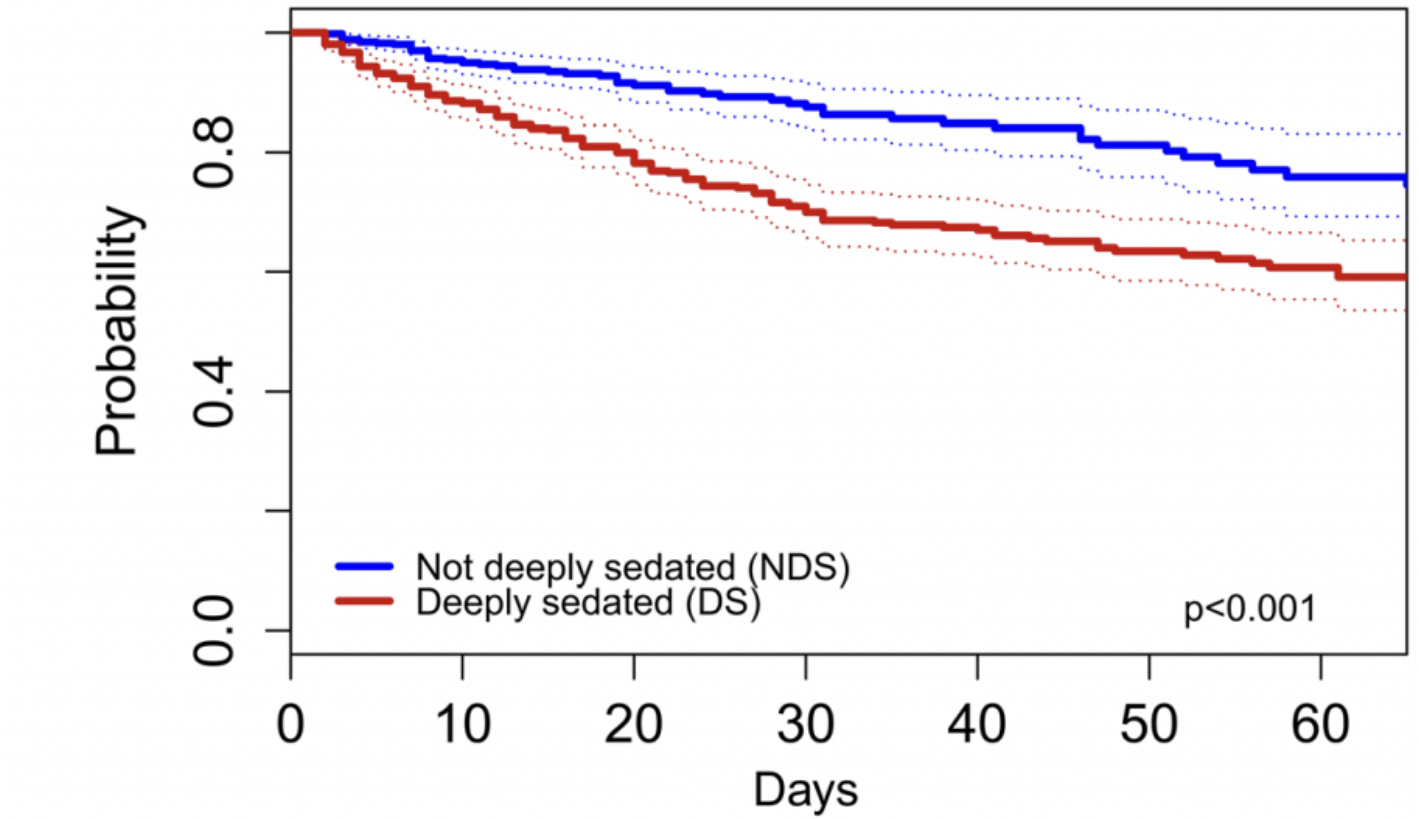
Light vs. Deep Sedation



In hospital survival HR 1.661

Balzer F. *Crit Care*. 2015;19:197

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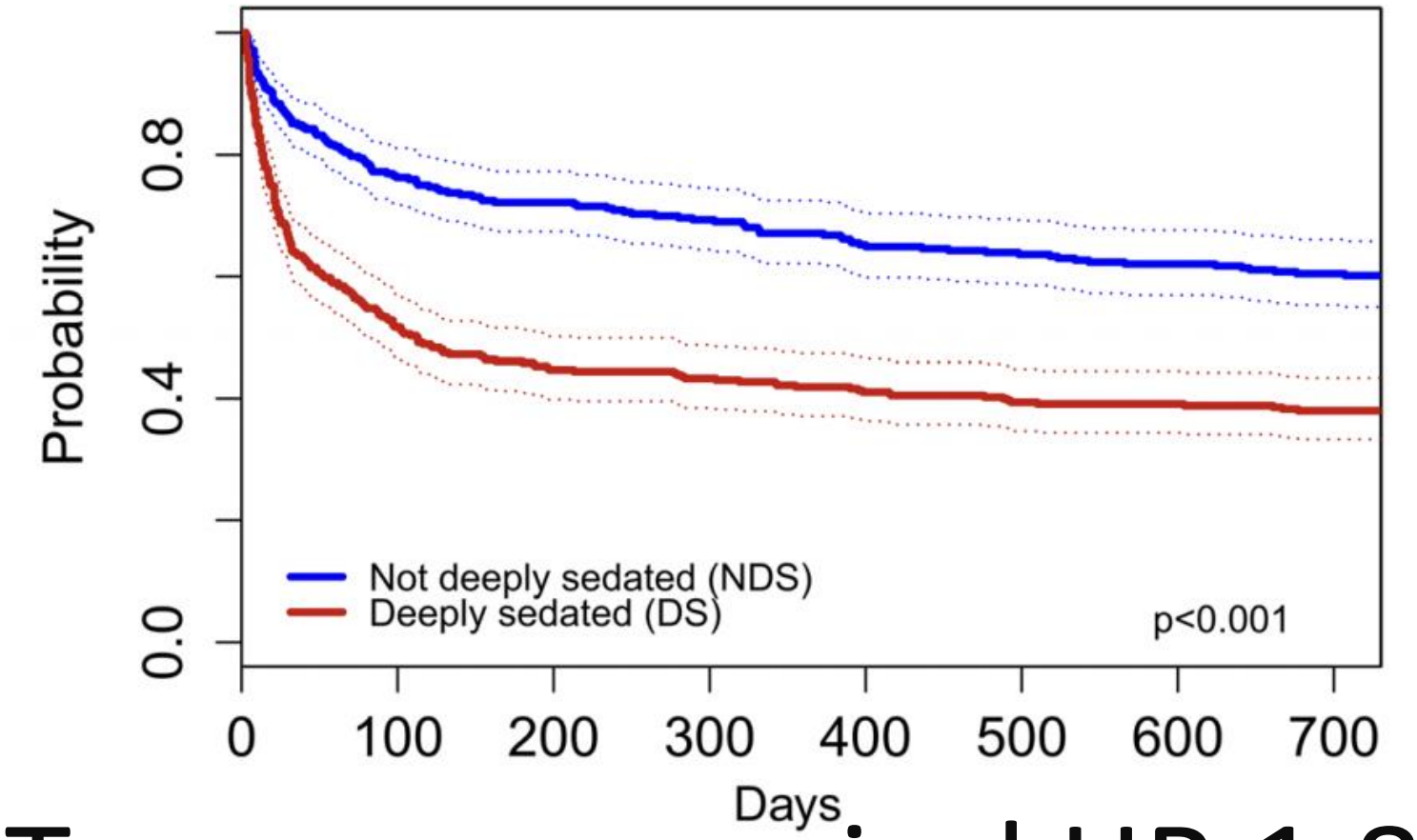
Light vs. Deep Sedation



Two-years survival HR 1.866

Balzer F. *Crit Care*. 2015;19:197

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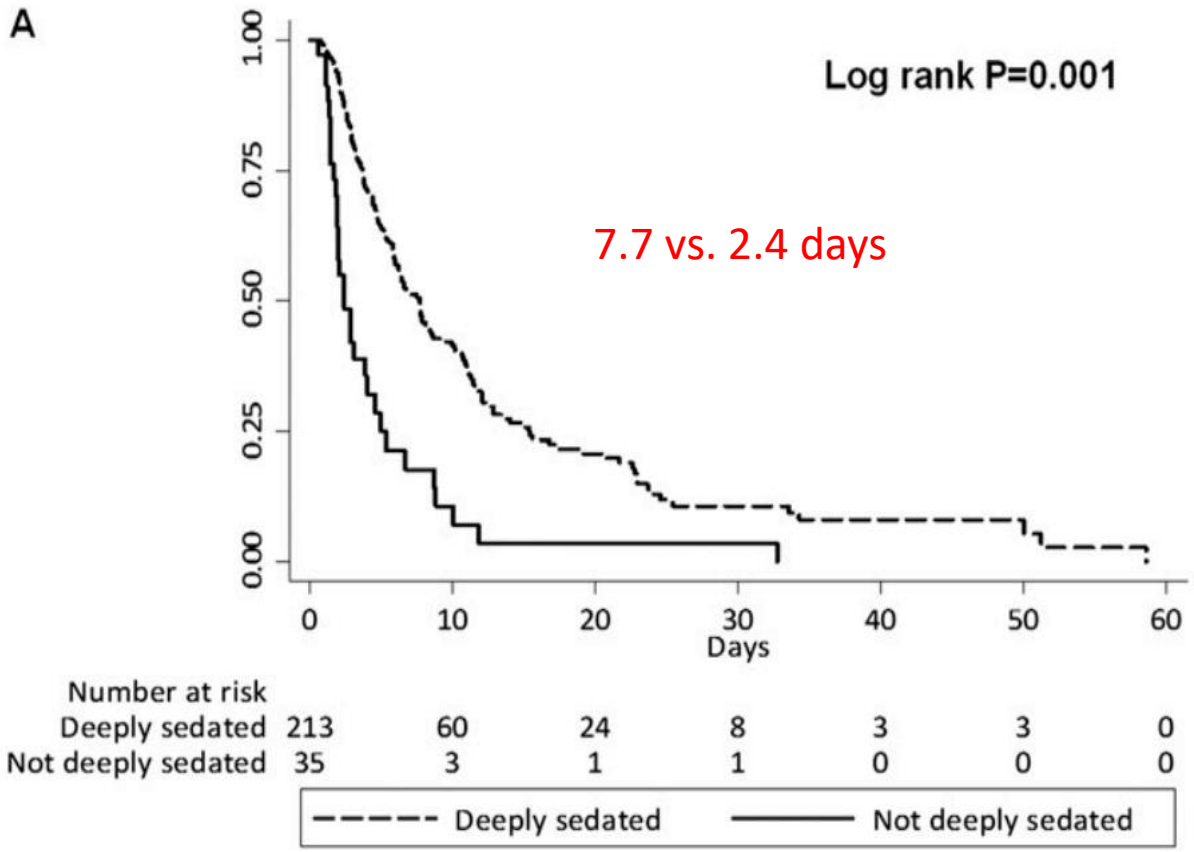
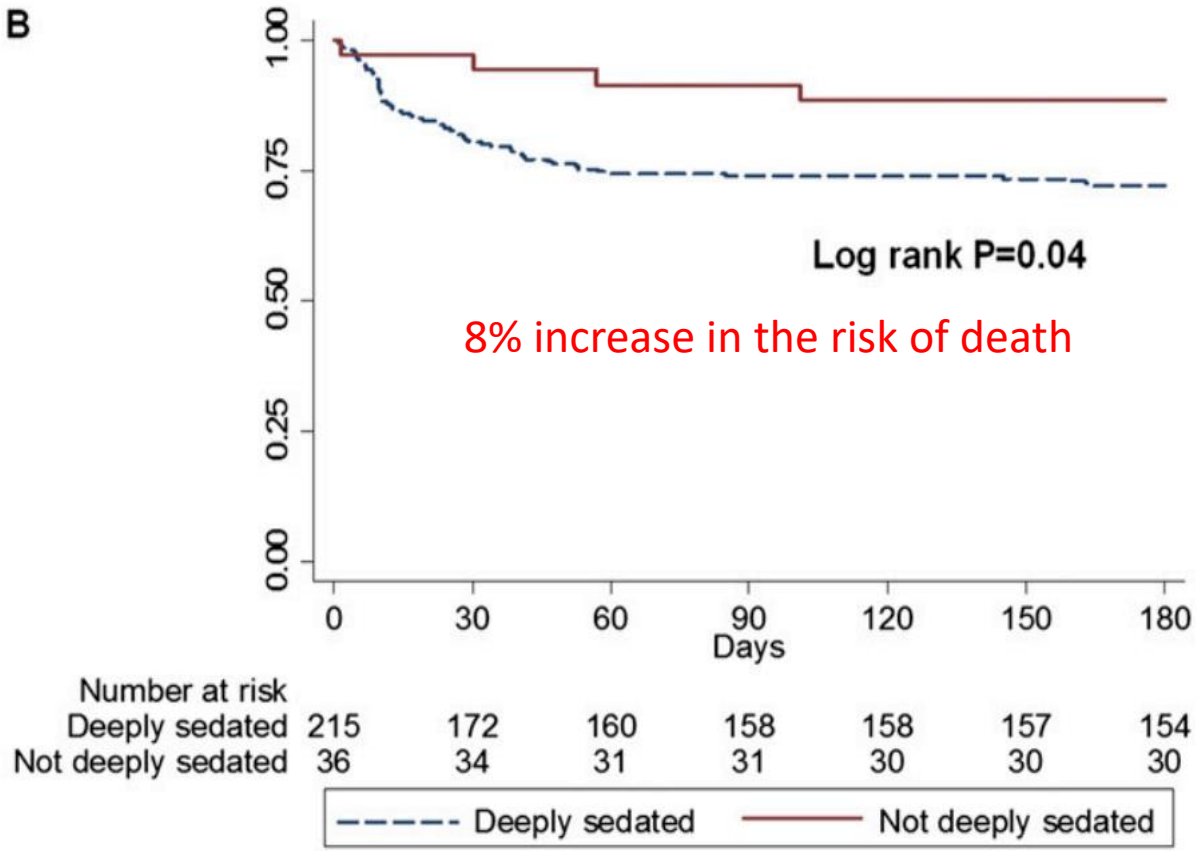
Light vs Deep Sedation in The MICU/SICU





Shehabi Y, et al. AJRCCM. 2012.

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Take-Home Message #1

- Light sedation when appropriate

- Deep sedation if:
  - Neuromuscular blockade
  - Intracranial hypertension
  - Severe respiratory failure
  - Refractory status epilepticus

Reade MC, Finfer S. N Engl J Med. 2014;370(5):444-454

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2018 PADIS Recommendations

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Devlin J, et al. Crit Care Med. 2018

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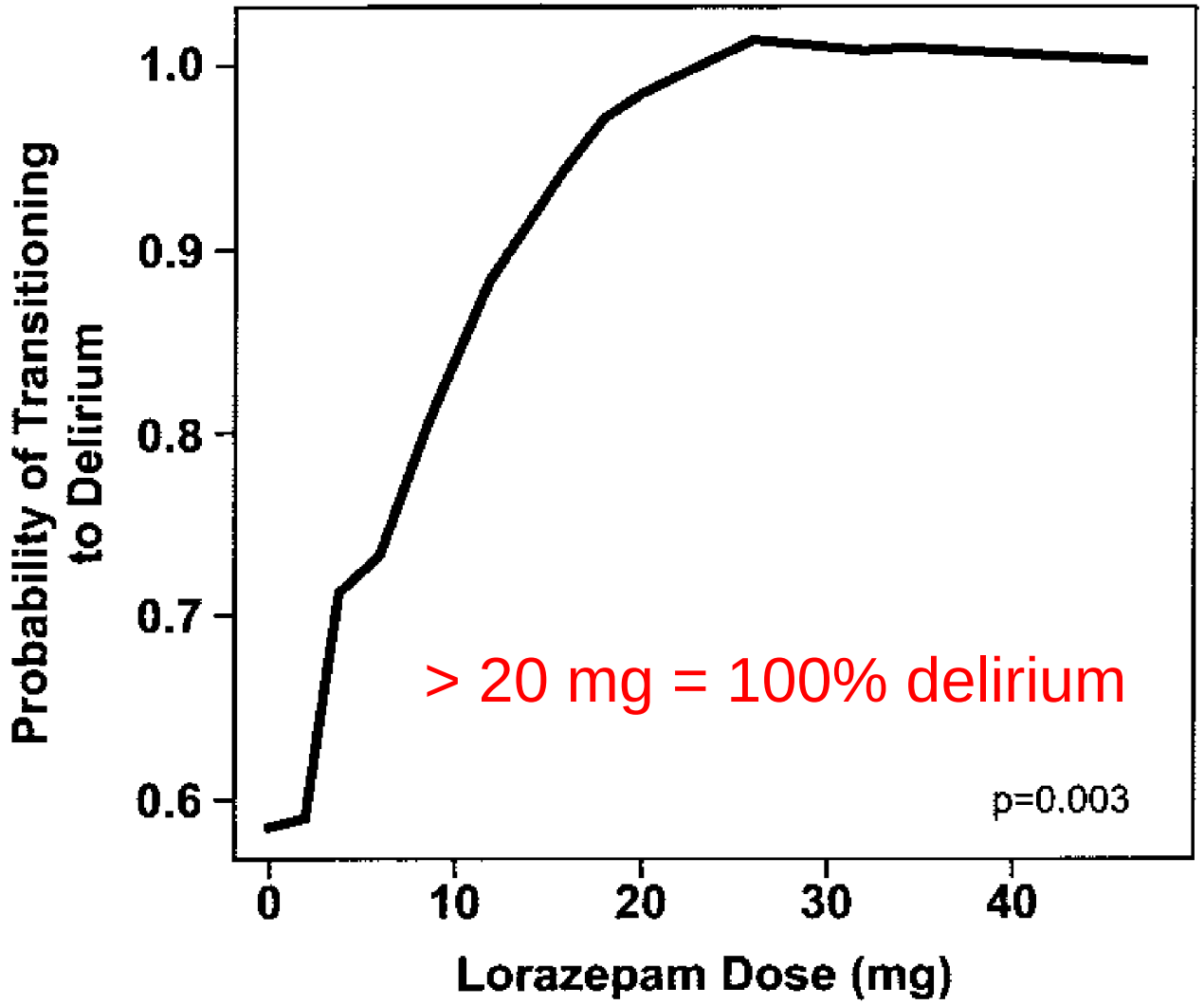
Benzodiazepines and Delirium



Anesthesiology 2006; 104:21-6

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MENDS Study

- Prospective, randomized, double blind
- MICU/SICU patients on ventilator >24 hours
- 106 patients
- Dexmedetomidine (DEX) infusion vs lorazepam infusion

Pandharipande PP, et al. JAMA. 2007

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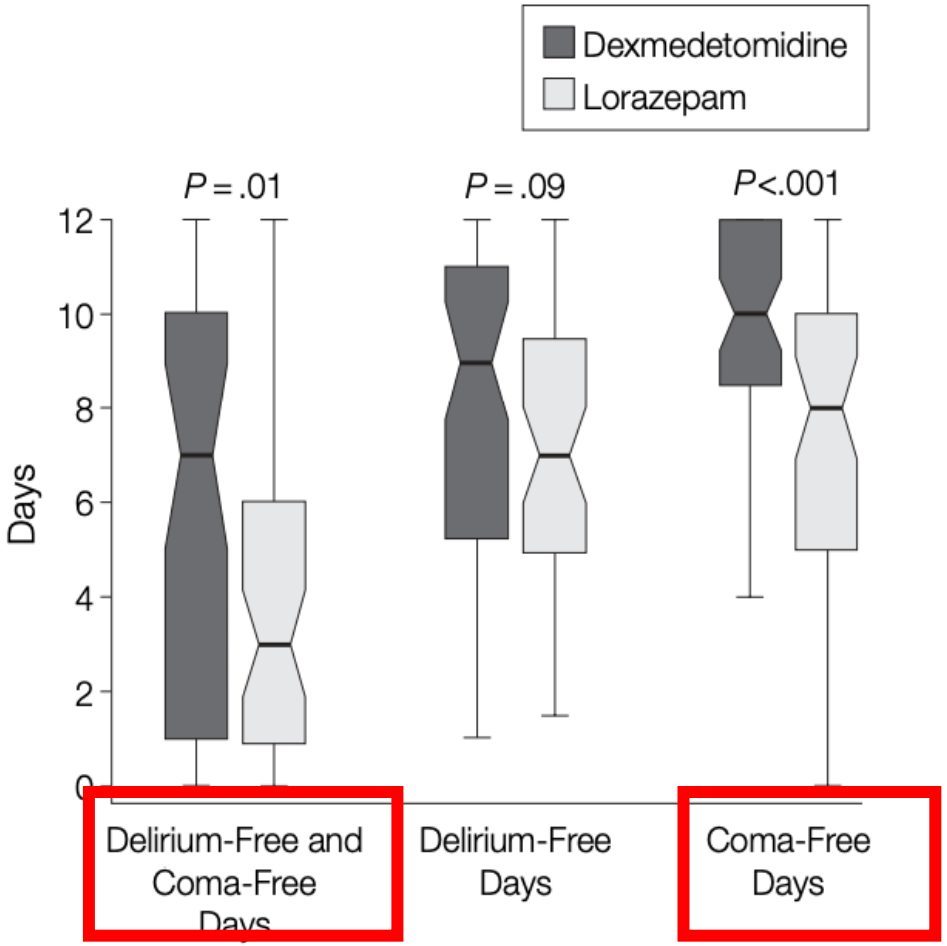
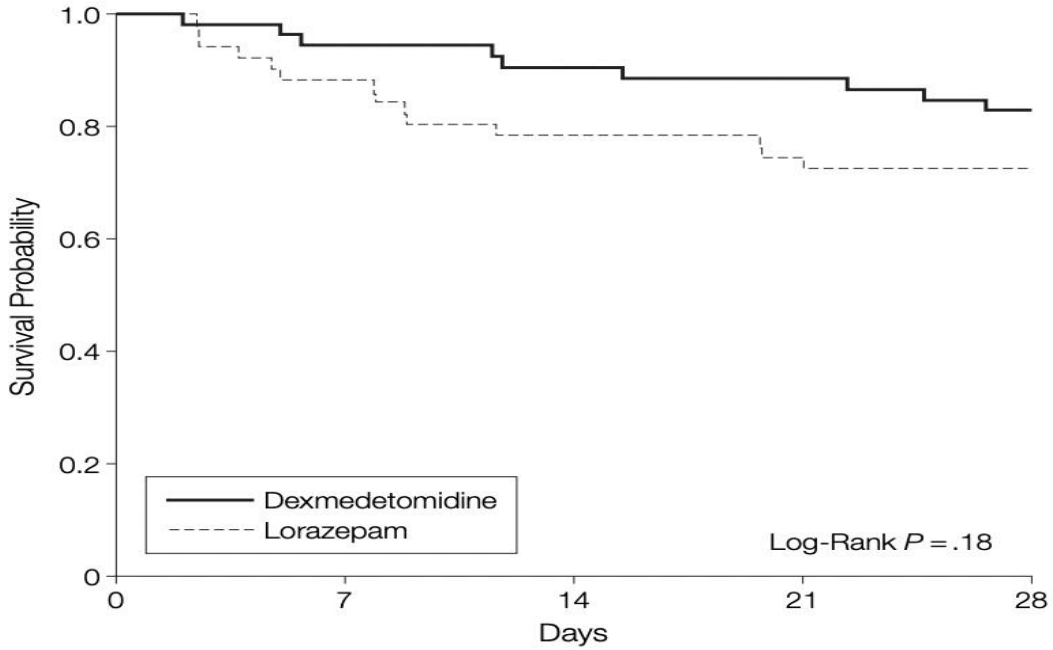
DEX had less delirium-free and coma-free days compared to lorazepam. However, both had similar survival rate





No. at Risk					
Dexmedetomidine	52	51	49	47	43
Lorazepam	51	45	41	38	37

Probability of survival during first 28 days after enrollment.

Pandharipande PP, et al. JAMA. 2007

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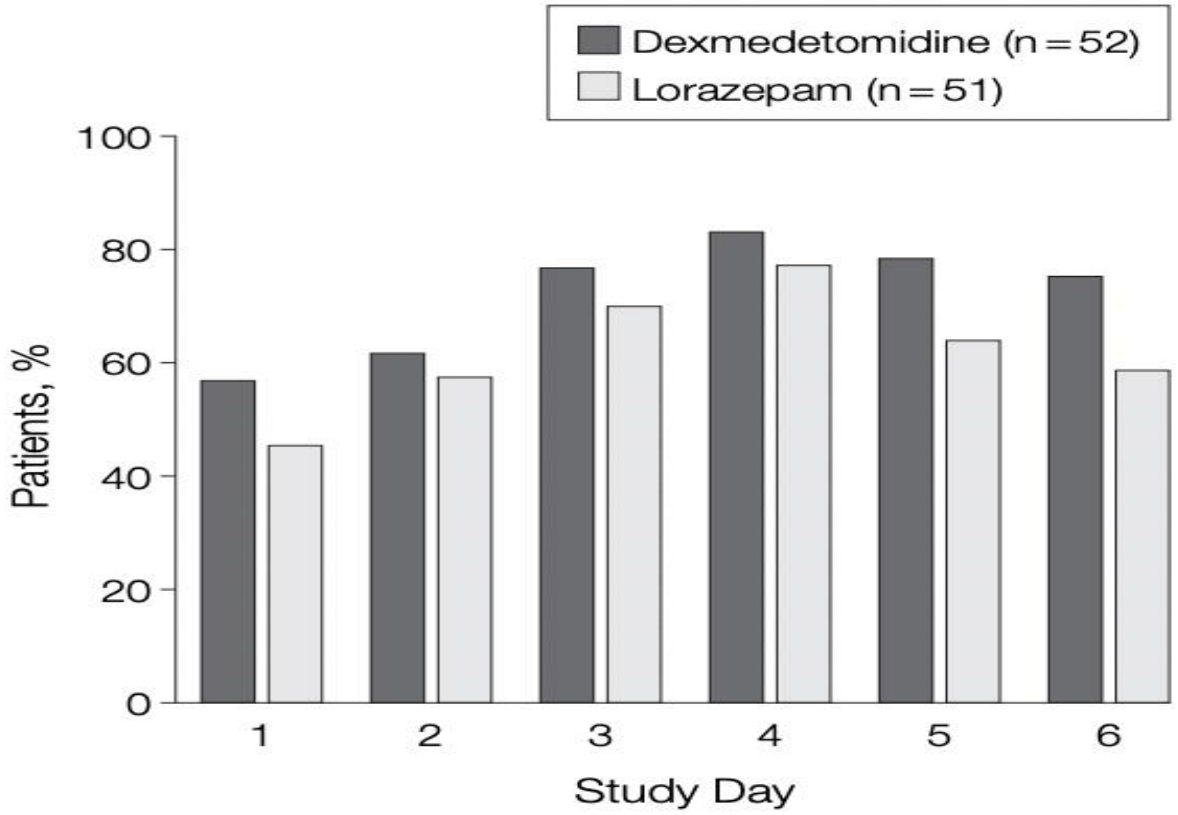
Dexmedetomidine-treated patients had a 4% to 17% greater likelihood of being at the target sedation score than lorazepam-treated patients



Pandharipande PP, et al. JAMA. 2007

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SEDCOM Study

- Prospective, randomized, double blind
- Included 297 adult patients expected to be on mechanical ventilation for ≥72 hours
- Dexmedetomidine vs midazolam

Riker R, et al. JAMA. 2009.

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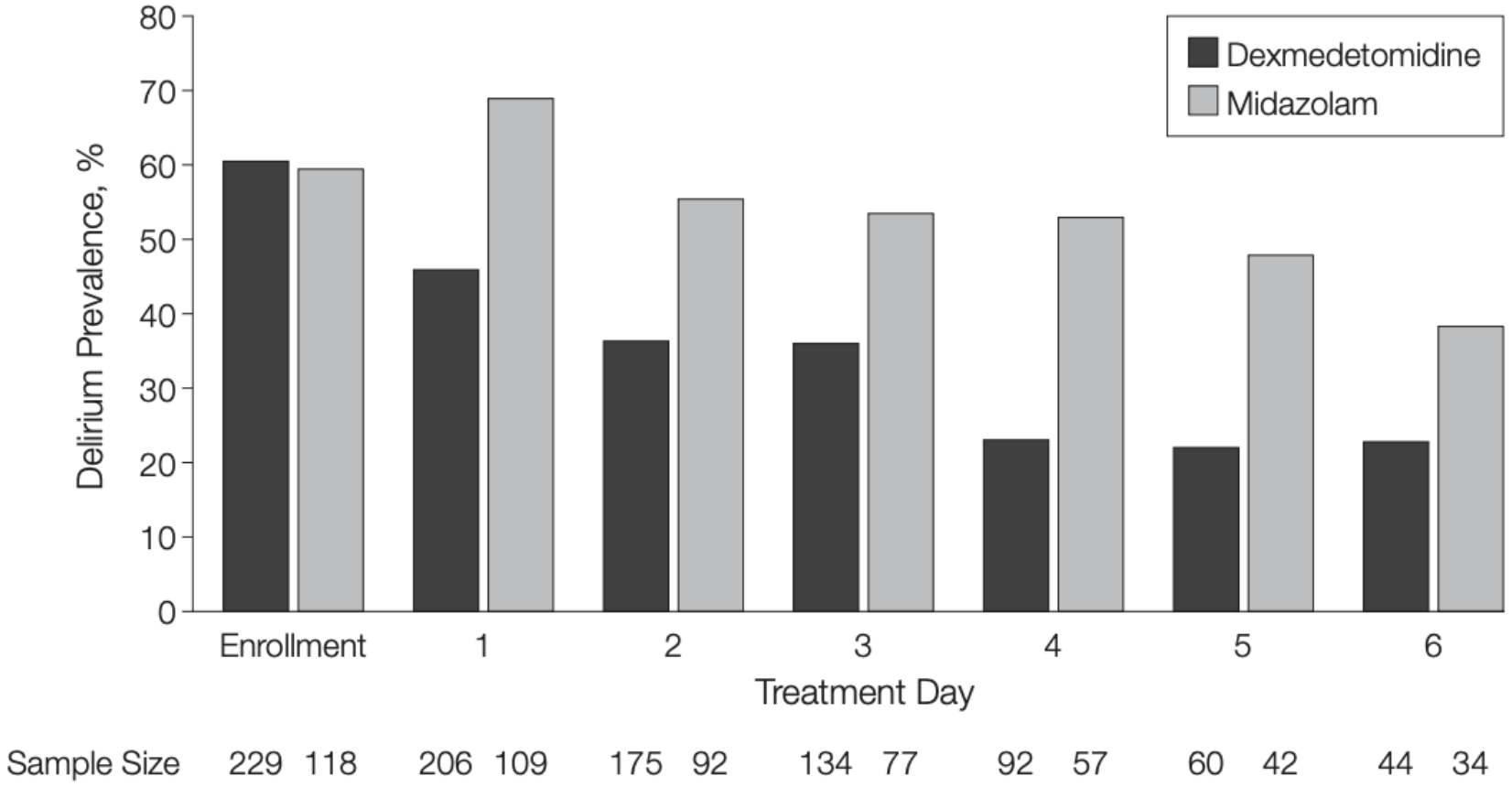
Prevalence of delirium among patients treated with dexmedetomidine vs midazolam



Riker R, et al. JAMA. 2009.

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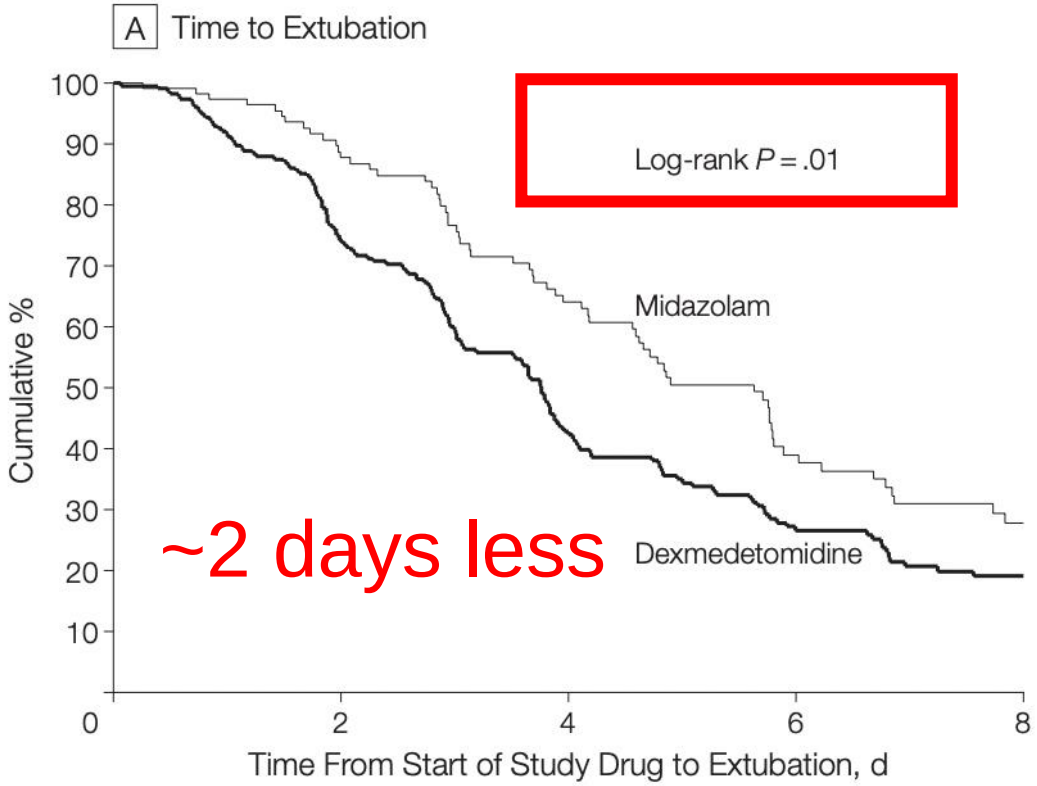

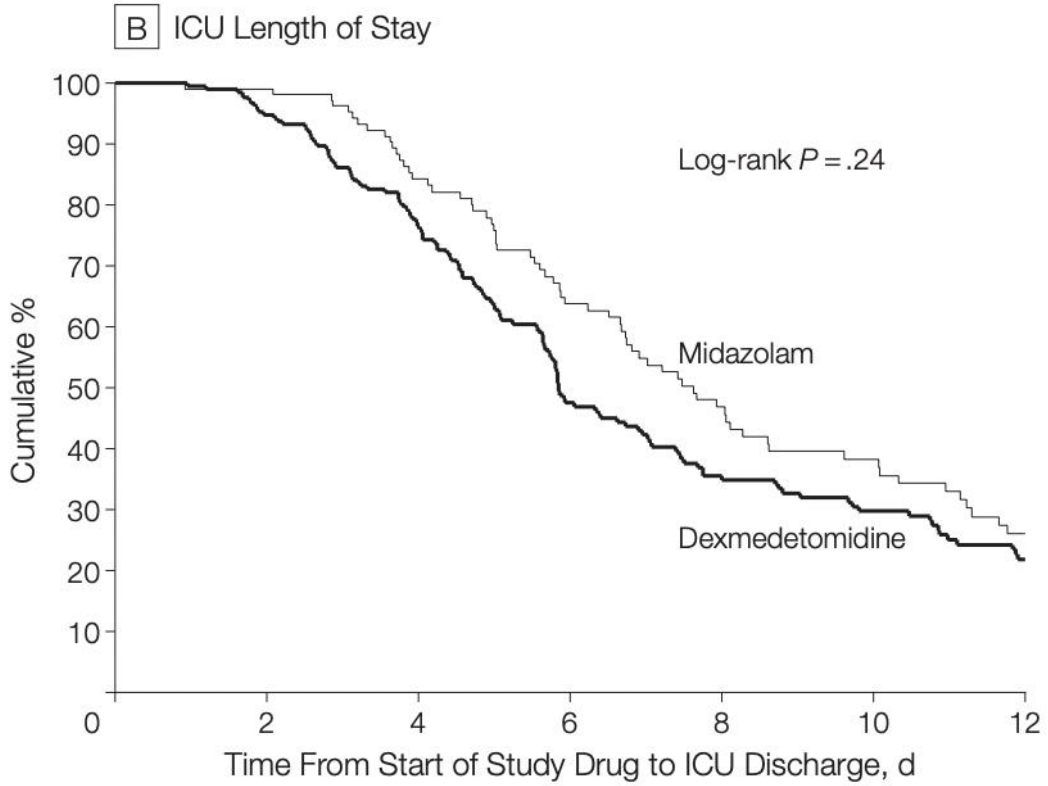

Riker R, et al. JAMA. 2009.

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Benzodiazepine vs. Nonbenzodiazepine

- Meta-Analysis of 6 randomized clinical trials
- Medical and surgical ICU patients on mechanical ventilation receiving intravenous sedation
- Benzodiazepine vs a nonbenzodiazepine

Fraser GL, et al. Crit Care Med. 2013.

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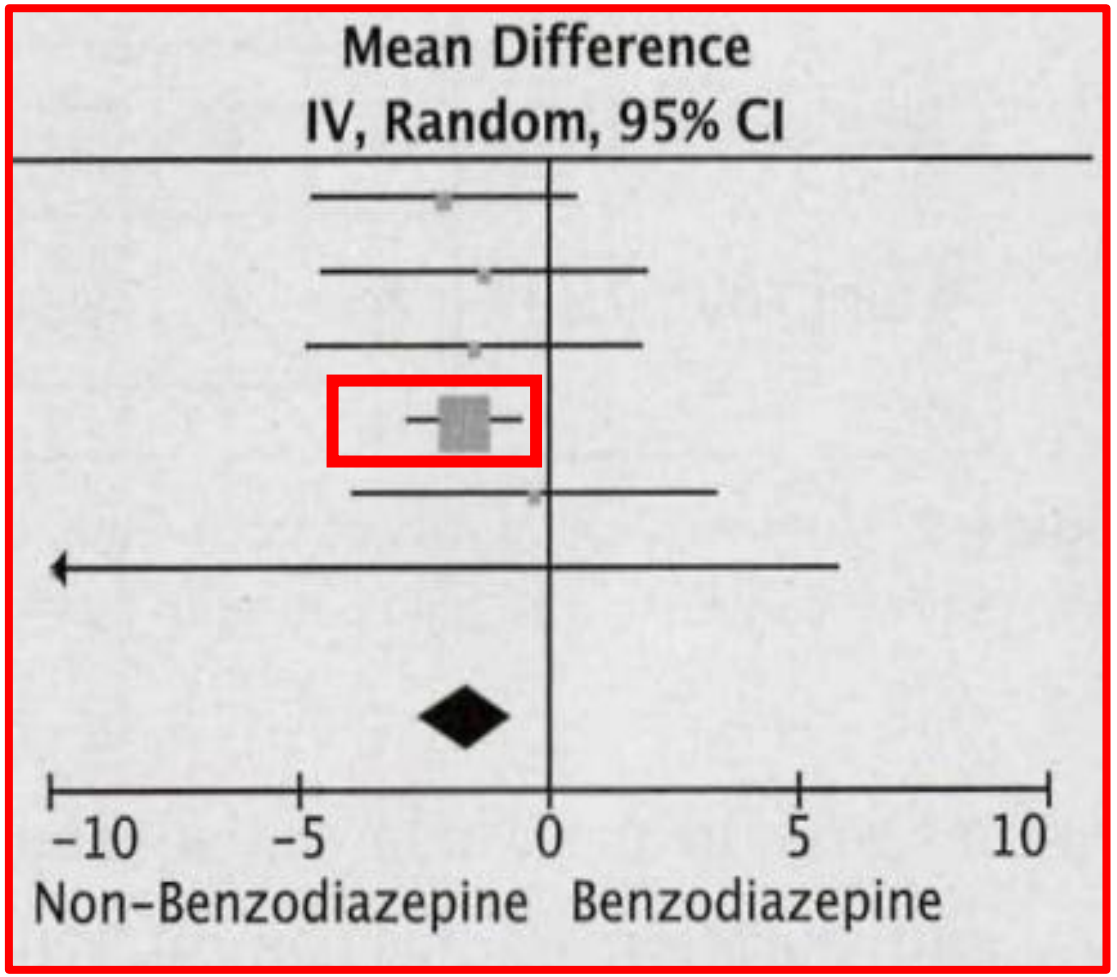
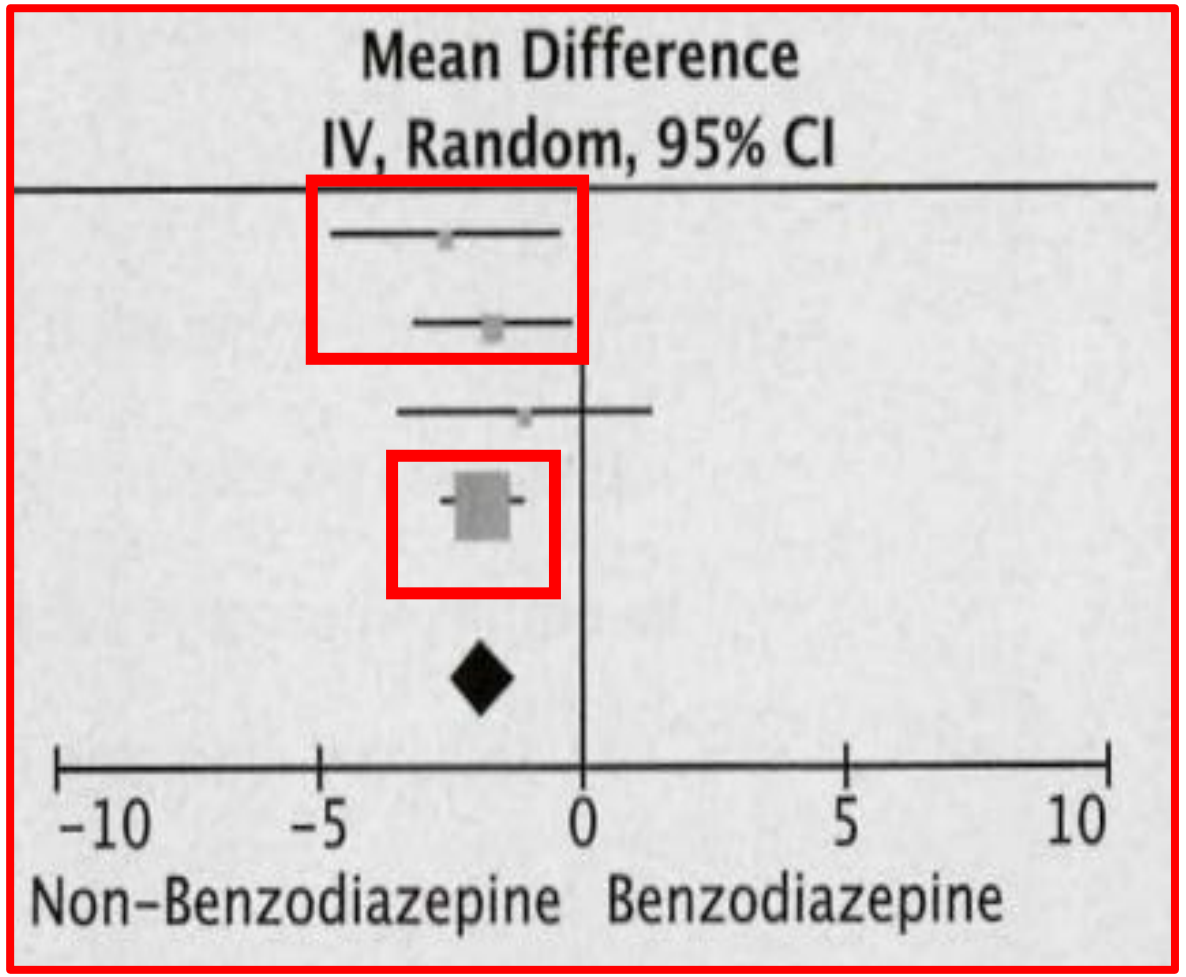
Benzodiazepine vs. Nonbenzodiazepine





Fraser GL, et al. Crit Care Med. 2013.

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MIDEX/PRODEX

- Adult ICU patients needing midazolam or propofol infusion for at least 24 hours

- Midazolam infusion for 249 patients (MIDEX)
- Propofol infusion for 251 patients (PRODEX)

vs.

- Dexmedetomidine

Jakob SM, et al. JAMA. 2012

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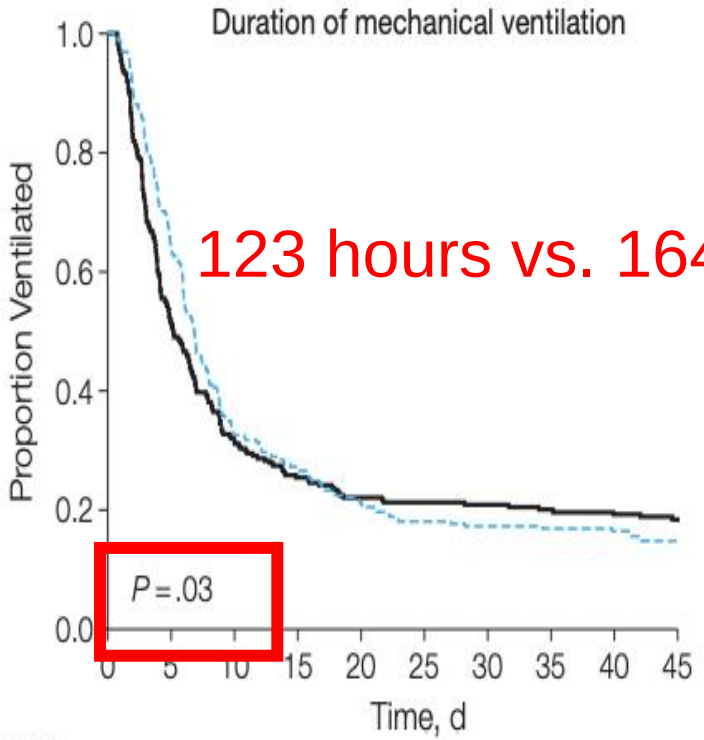
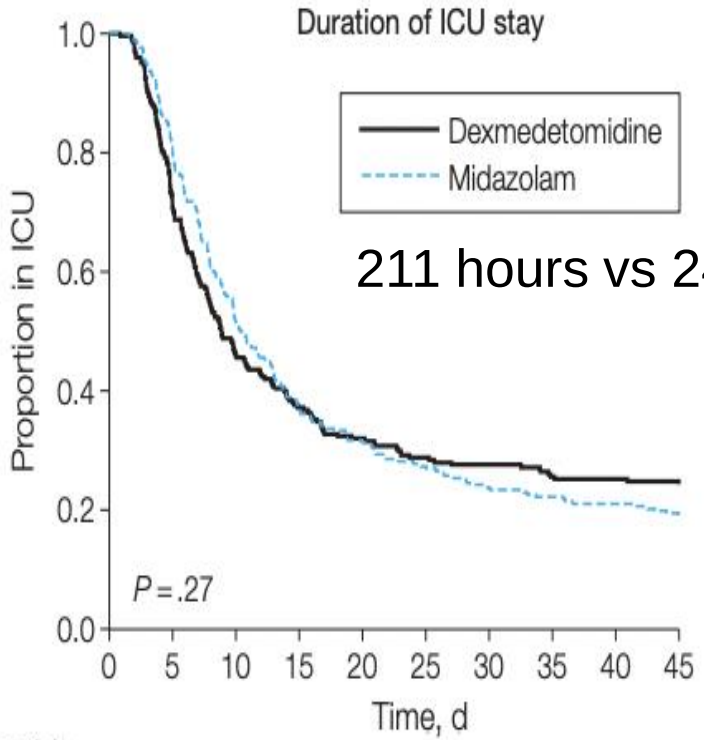
A MIDEX trial



123 hours vs. 164 hours

No. of patients at risk

Dexmedetomidine	249	128	77	62	54	52	51	49	47	43
Midazolam	251	162	81	68	53	45	43	41	40	34



211 hours vs 243 hours

No. of patients at risk

Dexmedetomidine	249	181	115	93	80	72	69	64	63	60
Midazolam	251	203	129	95	79	68	59	56	53	46

Jakob SM, et al. JAMA. 2012

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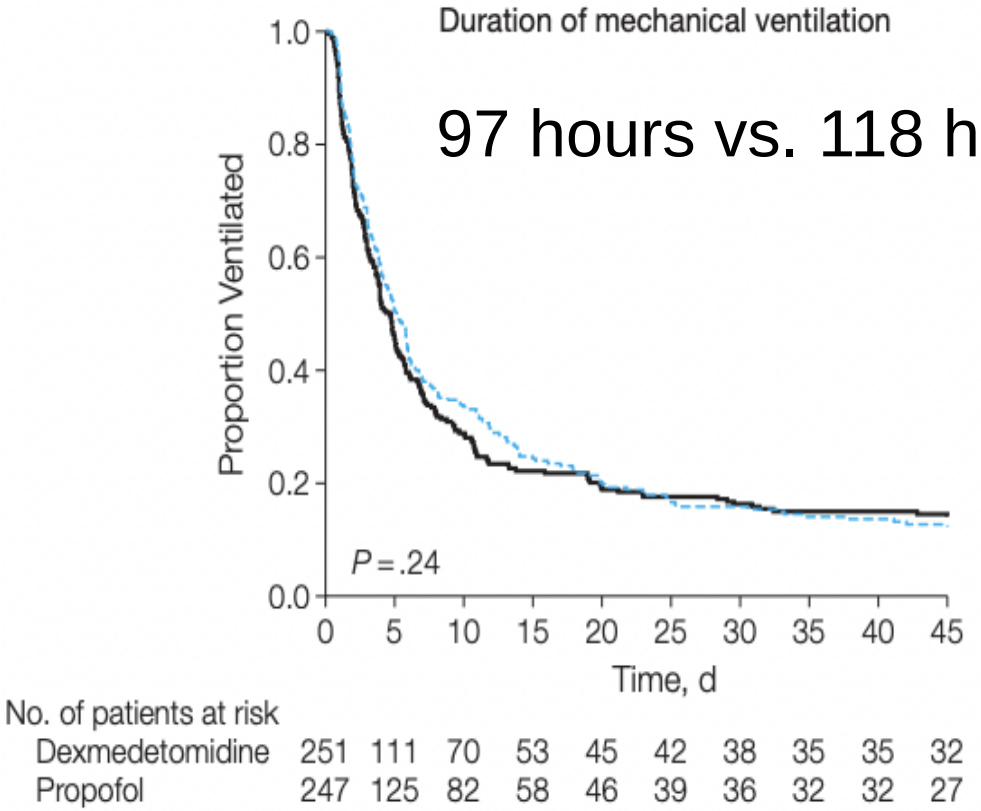
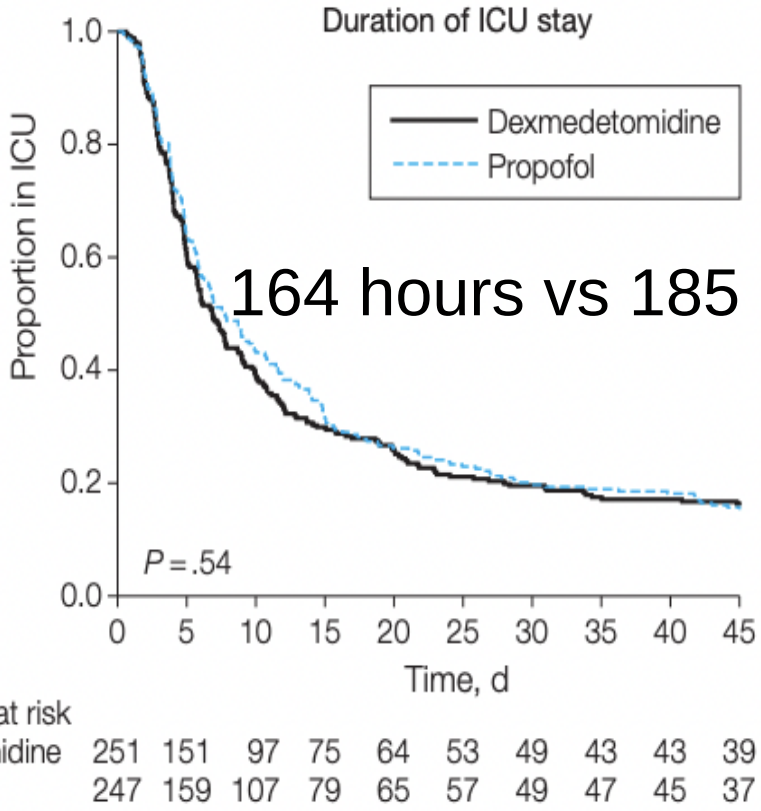
B PRODEX trial



97 hours vs. 118 hours

No. of patients at risk

Dexmedetomidine	251	111	70	53	45	42	38	35	35	32
Propofol	247	125	82	58	46	39	36	32	32	27



164 hours vs 185 hours

No. of patients at risk

Dexmedetomidine	251	151	97	75	64	53	49	43	43	39
Propofol	247	159	107	79	65	57	49	47	45	37

Jakob SM, et al. JAMA. 2012

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Take-Home Message #2

- Evidence showed less delirium, shorter duration of mechanical ventilation and ICU LOS with dexmedetomidine or propofol over benzodiazepines
- Similarities were found between propofol and dexmedetomidine (sedation goal?)
- Benzodiazepines if:
  - Status epilepticus
  - Alcohol withdrawal
  - Benzodiazepine dependence or withdrawal
  - Deep sedation or amnesia and with the use of neuromuscular blockade

Devlin J, et al. Crit Care Med. 2018

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The Ideal Agitation/Sedation Management

1. Treat pain
2. Treat pain
3. Treat pain

Analgosedation (analgesia-first)

4. Use validated scale for sedation-agitation (2-4 hours)
5. One size dose not fit all; patient specific approach
   - Over-sedation
   - Well-sedated
   - Under-sedation

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How to Put this Into Clinical Practice

- Treat pain, treat pain, then treat pain
- Remove reasons for irritation and agitation
- Determine your KEYSTONE sedative agent:
  - Level and duration of sedation
  - Other disease states, such as, seizure? Pancreatitis? Allergy? Elevated intracranial pressure? Severs ARDS?
- Clinical factors:
  - Blood pressure, heart rate, ventilation status (approaching extubation?)
- Organ dysfunctions:
  - Renal and hepatic
- Withdrawal:
  - Alcohol, home benzodiazepines

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How to Wean-Off Sedation?

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Spontaneous Awakening Trial (SAT)

1. Assess if patient is appropriate for SAT, then
2. Sedatives and analgesics should be stopped
3. Analgesics could be continued, as necessary if needed
4. Patient passes SAT if able to follow three out of four simple tasks:
   - Open their eyes
   - Look at their caregiver
   - Squeeze the hand,
   - Put out their tongue, or
   - Can go without sedation for 4 hours or more without the following:
     - Constant anxiety, agitation, or pain
     - Respiratory rate of 35 breaths/minute for at least 5 minutes
     - Oxygen saturation (SpO2) of < 88% for at least 5 minutes
     - Acute cardiac dysrhythmia or respiratory distress

Girard TD. Lancet. 2008;371(9607):126-134
AHRQ Pub. No. 16(17)-0018-17-EF
January 2017

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Spontaneous Awakening Trial (SAT)

- SAT could be deferred if any presents:
  - Current RASS is >2
  - The goal is deep sedation
  - Actively seizing
  - Active alcohol withdrawal
  - Active sedative agent dose escalation
  - FiO2 >50%
  - Neuromuscular blocker use
  - Increased intracranial pressure

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