ICU Sedation in 2019
Lessons Learned

Richard R. Riker MD, FCCM
Director, Medical Critical Care

Maine Medical Center
Portland, Maine USA
Professor of Medicine
Tufts University School of Medicine

Sedation Lessons Learned

1. Older and More Recent Studies

2. Key Concepts
   A. Control group is critical
   B. Targeted level of sedation
   C. Sedative versus other drug/therapy
   D. Timing is everything
   E. Provocative questions

Table 2. Summary of Selected Trials Assessing the Effectiveness of Sedative Agents Used in the ICU* (cont)

Study/Patient Population†	Length of Sedation	Sedation Score Target Level	Sedatives‡	Mean Dosage	Mean % Time at Sedation Target Level§	Time to Extubation, min	Length of Ventilation, h	ICU Length of Stay, d
Propofol vs Midazolam (Mixed ICU Patients)								
Costa et al,[33] 1994								
Mixed ICU (n = 139)	Short (<72 h)	RC scale	Propofol (c) Midazolam (c) Diazepam (i) + Morphine (i)	16.6-50 μg/kg/min 1.7-3.3 μg/kg/min 0.2-0.3 mg/kg 0.15-0.22 mg/kg	94 83 (*P*<.05) 38 (no statistics)‖	120 432 594 (*P*<.05)	NA	"Shorter stay in P group" (no data)
(n = 213)	(>72 h)		Propofol (c) Midazolam (c)	16.6-50 μg/kg/min 1.7-3.3 μg/kg/min	Better sedation in P group (no statistics)‖	Shorter in P group (no statistics)‖	NA	NA
Ronan et al,[34] 1995								
Postoperative (n = 60)	Short (24 h)	RL 3	Propofol (c) Midazolam (c)	24 μg/kg/min 2.1 mg/h	No difference	NA	NA	NA
Kress et al,[35] 1996								
Medical ICU (n = 73) (x = 48)	Up to 3 d	Study-specific scale	Propofol (c) Midazolam (c)	20.9 μg/kg/min 3.1 mg/h	Time to sedation: 20.4 min 16 min (*P* = .30) [n = 39]	NA	NA	NA
Chamorro et al,[36] 1996								
Mixed ICU (n = 98)	Medium/ long (2-5 d)	Study-specific scales	Propofol (c) Midazolam (c)	46.7 μg/kg/min 2.3 μg/kg/min	76.5 66.2 (*P*<.01)	NA	NA	NA
Barrientos-Vega et al,[37] 1997								
Mixed ICU (x = 121) (n = 108)	Medium/ long (24 h-9 d)	RL 4-5	Propofol (c) Midazolam (c)	51.2-95 μg/kg/min¶ 3.1-7.2 μg/kg/min¶	% of patients at target level: 66; 57(NSD)	2088 5874 (*P*<.001) [y = 52]	NA	NA
Weinbroum et al,[38] 1997								
Mixed ICU (n = 67)	3-8 d	Study-specific scale	Propofol (c) Midazolam (c)	30 μg/kg/min 1.2 μg/kg/min in P group (*P*<.01)	No difference in level of sedation, more agitation	NA	NA	31 21 (No statistics)‖
Sanchez-Izquierdo et al,[39] 1998								
Trauma ICU (x = 106) (n = 100)	2-24 d	Simplified RL 3-4	Propofol (c) Midazolam (c) Midazolam (c)+ Propofol (c)	35.3 μg/kg/min 3.2 μg/kg/min 2.3 μg/kg/min 26.7 μg/kg/min	87 85 90 (NSD)	NA	NA	18 24 17 (NSD)
Midazolam vs Lorazepam (Mixed ICU Patients)								
Pohlman et al,[40] 1994								
Medical ICU (n = 20)	2-10 d	RL 2-3	Midazolam (c+i) Lorazepam (c+i)	0.2 mg/kg/h 0.1 mg/kg/h	No difference in time to sedation; time to return to baseline mental status: M, 1815 min; L, 261 min (NSD)	NA	NA	NA
Cernaianu et al,[41] 1996								
Mixed ICU (n = 95)	Short (8 h)	Study-specific scale	Midazolam (c) Lorazepam (i)	1.8 mg/h 0.2 mg/h	NSD (no data)	NA	NA	NA
Benzodiazepine vs Isoflurane								
Kong et al,[42] 1989								
Mixed ICU (n = 60)	Short (≤24 h)	RL 2-4	Midazolam (c) Isoflurane (inh)	3.1 mg/h 0.2%	64 86 (*P*<.001)	195 60 (*P*<.001) [y = 27]	NA	NA
Spencer and Willatts,[43] 1992								
Mixed ICU (n = 60)	4 h-6 d	RL 2-4	Midazolam (c) Isoflurane (inh)	3.1 mg/h 0.3%	67 70 (NSD)	900 54 (*P*<.001)	NA	2.02 2.08 (NSD)

Ostermann ME. JAMA 2000

More Recent ICU Sedation Studies:

	MENDS	SEDCOM	MIDEX	PRODEX	SPICE
Enrollment	8/04 – 4/06	3/05 – 8/07	2007-2010		11/13 - 2/18
# Ctrs/Pts	2/106	65/366	44/500	31/498	74/3918
Intervention	Dex:Loraz	2:1 Dex:Mid	Dex:Mid	Dex:Prop	EGDS:SC
1° Outcome	12d DFCF	%Time Target	%Time Trgt Noninferior	%Time Trgt Noninferior	90d All-C Mortality

Control Group is Critical

DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

JOHN P. KRESS, M.D., ANNE S. POHLMAN, R.N., MICHAEL F. O'CONNOR, M.D., AND JESSE B. HALL, M.D.

- RCT to daily interruption or standard sedation, randomized to midazolam or propofol starting 48 hrs after enrollment
- Target – Ramsay 3 (responsive to commands only) or 4 (asleep, brisk response to a light glabellar tap or loud sound)
- Interrupted midazolam/propofol and morphine daily until patients awake (3 of 4 instructions) or became agitated
- Sedative infusions restarted at half the previous rates and were adjusted according to the need for sedation.

Kress. N Engl J Med 2000; 342:1471

Control Group is Critical

- 128 adults continuous infusion sedation drugs
- Daily wake-up versus standard care
- Daily wake-up shortened:
  duration ventilation: 4.9 vs 7.3 days, p=0.004
  median ICU LOS: 6.4 vs 9.9 days, p=0.02
  diagnostic testing: 9% vs 27%, p=0.02

- % days patients were awake while receiving a sedative infusion 85.5% vs 9.0%, p<0.001

Kress. N Engl J Med 2000; 342:1471

Control Group is Critical

Variable	Intervention Group (N=68)	Control Group (N=60)	P Value
	median (interquartile range)		
Duration of mechanical ventilation (days)	4.9 (2.5–8.6)	7.3 (3.4–16.1)	0.004
Length of stay (days)			
Intensive care unit	6.4 (3.9–12.0)	9.9 (4.7–17.9)	0.02
Hospital	13.3 (7.3–20.0)	16.9 (8.5–26.6)	0.19
Midazolam subgroup (no. of patients)	37	29	
Total dose of midazolam (mg)	229.8 (59–491)	425.5 (208–824)	0.05
Average rate of midazolam infusion (mg/kg/hr)	0.032 (0.02–0.05)	0.054 (0.03–0.07)	0.06
Total dose of morphine (mg)	205 (68–393)	481 (239–748)	0.009
Average rate of morphine infusion (mg/kg/hr)	0.027 (0.02–0.04)	0.05 (0.04–0.07)	0.004
Propofol subgroup (no. of patients)	31	31	
Total dose of propofol (mg)	15,150 (3983–34,125)	17,588 (4769–35,619)	0.54
Average rate of propofol infusion (mg/kg/hr)	1.9 (0.9–2.6)	1.4 (0.9–2.4)	0.41
Total dose of morphine (mg)	352 (108–632)	382 (148–1053)	0.33
Average rate of morphine infusion (mg/kg/hr)	0.035 (0.02–0.07)	0.043 (0.02–0.07)	0.65

Kress. N Engl J Med 2000; 342:1471

Control Group is Critical

Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol

A Randomized Controlled Trial

Sangeeta Mehta, MD
Lisa Burry, PharmD
Deborah Cook, MD
Dean Fergusson, PhD
Marilyn Steinberg, RN
John Granton, MD
Margaret Herridge, MD
Niall Ferguson, MD
John Devlin, PharmD
Maged Tanios, MD
Peter Dodek, MD
Robert Fowler, MD
Karen Burns, MD
Michael Jacka, MD
Kendiss Olafson, MD
Yoanna Skrobik, MD
Paul Hébert, MD
Elham Sabri, MSc
Maureen Meade, MD
for the SLEAP Investigators and the Canadian Critical Care Trials Group

- N=423 Jan 2008-July 2011
- Meds not controlled
- Target lighter sedation
  - SAS 3-4 or RASS –3 to 0
- Same interruption protocol as Kress

Mehta S. JAMA 2012; 308:1985-92

Control Group is Critical

- SAS scores were similar
  - 3.28 [2.92 - 3.85] Interrupt
  - 3.23 [3.0 - 3.71] Standard
  - Δ 0.05 [−0.10-0.19], p=0.52

- No difference T2Ext or other outcomes
- Increased sedation doses with interruption
- Increased nurse workload with interruption

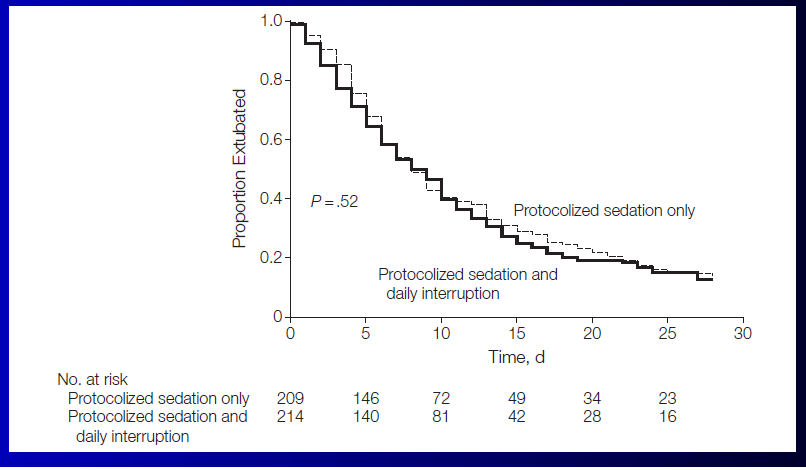


Table 2. Patient Outcomes

	Protocolized Sedation and Interruption (n = 214)	Protocolized Sedation (n = 209)	Measure of Effect (95% CI)	*P* Value
Days to successful extubation, median (IQR)[a]	7 (4 to 13)	7 (3 to 12)	HR, 1.08 (0.86 to 1.35)	.52
Days in ICU,[b] median (IQR)[a]	10 (5 to 17)	10 (6 to 20)	Mean difference, −3.17 (−6.89 to 0.55)	.36
Days in hospital, median (IQR)[a]	20 (10 to 36)	20 (10 to 48)	Mean difference, −8.2 (−17.64 to 1.19)	.42
ICU mortality, No. (%)	50 (23.4)	52 (24.9)	RR, 0.94 (0.67 to 1.32)	.72
Hospital mortality, No. (%)	63 (29.6)	63 (30.1)	RR, 0.98 (0.73 to 1.31)	.89
ICU-acquired organ failure and supportive therapies, No. (%)				
ARDS	89 (41.8)	78 (37.3)	RR, 1.12 (0.88 to 1.42)	.35
Vasopressors/inotropes	121 (56.8)	130 (62.2)	RR, 0.91 (0.78 to 1.07)	.26
Renal replacement	50 (23.5)	37 (17.7)	RR, 1.33 (0.91 to 1.94)	.14
Neuromuscular blockade	20 (9.7)	21 (10.2)	RR, 0.94 (0.53 to 1.69)	.84
Unintentional device removal, No. (%)				
Gastric tube	18 (8.5)	29 (13.9)	RR, 0.61 (0.35 to 1.07)	.08
Endotracheal tube	10 (4.7)	12 (5.8)	RR, 0.82 (0.36 to 1.84)	.64
Urinary catheter	6 (2.8)	13 (6.2)	RR, 0.45 (0.17 to 1.17)	.09
Central venous or arterial catheter	17 (8.0)	10 (4.8)	RR, 1.68 (0.79 to 3.57)	.18
Neuroimaging in ICU, No. (%)				
Computed tomography	29 (13.6)	33 (15.9)	RR, 0.85 (0.54 to 1.35)	.53
Magnetic resonance imaging	9 (4.2)	7 (3.4)	RR, 1.25 (0.47 to 3.29)	.64
Physical restraint				
Patients, No. (%)	166 (76.4)	166 (79.4)	RR, 0.96 (0.87 to 1.07)	.46
Study days, mean (SD)	4.71 (5.67)	5.36 (6.14)	Mean difference, −0.70 (−1.84 to 0.43)	
Delirium, No (%)[b]	113 (53.3)	113 (54.1)	RR, 0.98 (0.82 to 1.17)	.83
Reintubation within 48 h, No. (%)	12 (5.6)	16 (7.7)	RR, 0.73 (0.35 to 1.50)	.39
Tracheostomy, No (%)	49 (23.2)	54 (26.3)	RR, 0.88 (0.63 to 1.23)	.46

Mehta S. JAMA 2012; 308:1985-92

Control Group is Critical

Table 3. Benzodiazepine and Opioid Administration[a]

	Protocolized Sedation and Interruption (n = 214)	Protocolized Sedation (n = 209)	Measure of Effect, Mean Difference (95% CI)	*P* Value
Midazolam equivalents				
Total dose/patient, mg	1087 (4297) 222 (50 to 734)	1038 (4592) 237 (57 to 599)	48.4 (–804.4 to 901.2)	.91
Dose/patient/d, mg	102 (326) 8 (0 to 86)	82 (287) 0 (0 to 50)	19.23 (2.37 to 37.07)	.04
Dose/patient/d, infusion, mg	101 (325) 6 (0 to 86)	82 (287) 0 (0 to 50)	19.22 (1.92 to 36.53)	.03
Dose/patient/d, bolus, mg	0.99 (5.9) 0 (0 to 0)	0.49 (2.65) 0 (0 to 0)	0.50 (0.23 to 0.76)	<.001
Infusion, d	5.73 (6.42) 4 (2 to 7)	5.58 (5.91) 4 (2 to 7)	0.15 (–1.04 to 1.33)	.81
Boluses/d, No.	0.253 (1.145) 0 (0 to 0)	0.177 (0.808) 0 (0 to 0)	0.077 (0.020 to 0.134)	.007
Fentanyl equivalents				
Total dose/patient, µg	18 997 (59 928) 5286 (1512 to 16 437)	13 532 (23 219) 5936 (2056 to 15 236)	5464.6 (–3236.0 to 14 165.2)	.22
Dose/patient/d, µg	1780 (4135) 550 (50 to 1850)	1070 (2066) 260 (0 to 1400)	709.3 (522.0 to 897.7)	<.001
Dose/patient/d, infusion, µg	1664 (4070) 420 (0 to 1725)	984 (2002) 80 (0 to 1260)	679.7 (495.3 to 864.1)	<.001
Dose/patient/d bolus, µg	116 (215) 0 (0 to 100)	86 (169) 40 (0 to 150)	30.13 (19.15 to 41.11)	<.001
Infusion, d	6.44 (6.86) 5 (2 to 9)	6.61 (6.20) 5 (3 to 9)	–0.17 (–1.42 to 1.09)	.79
Boluses/d, No.	2.18 (2.87) 1 (0 to 4)	1.79 (2.67) 0 (0 to 3)	0.395 (0.239 to 0.551)	<.001

Mehta. JAMA 2012; 308:1985-92

Partial Liquid Ventilation – Control group did exceedingly well

EGDT Sepsis – Control group did exceedingly poorly

Level of Sedation

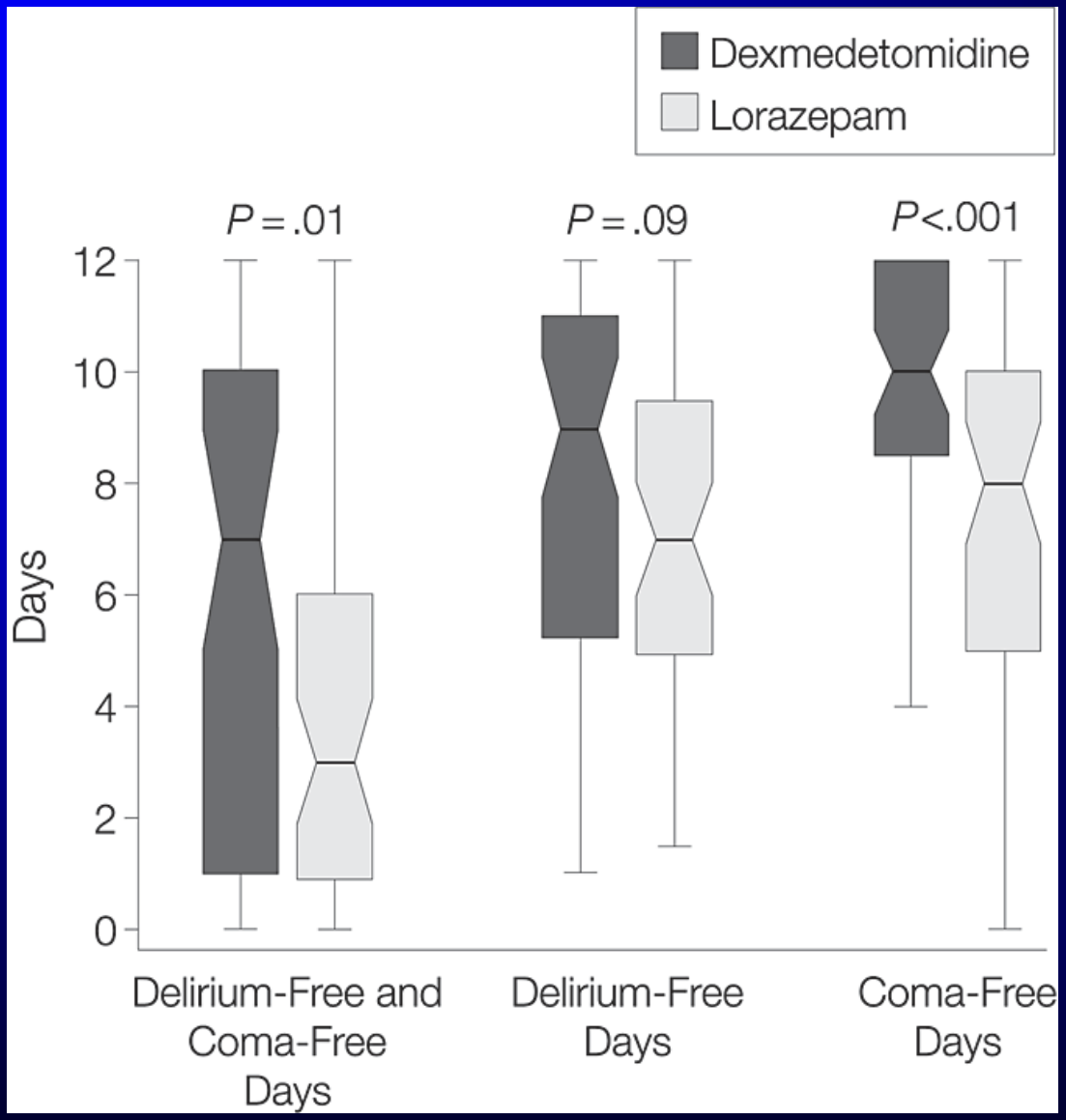
Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial

- RCT 106 patients - Lorazepam vs Dexmedetomidine
- RASS target determined by clinical team, later categorized
  - Deep = RASS -3, -4, -5
  - Light = RASS 0, -1, -2
- Dexmedetomidine more days without coma or delirium-coma
- No difference ventilator-free days, ICU LOS, 28-day mortality

Pandharipande. JAMA 2007; 298:2644

Level of Sedation



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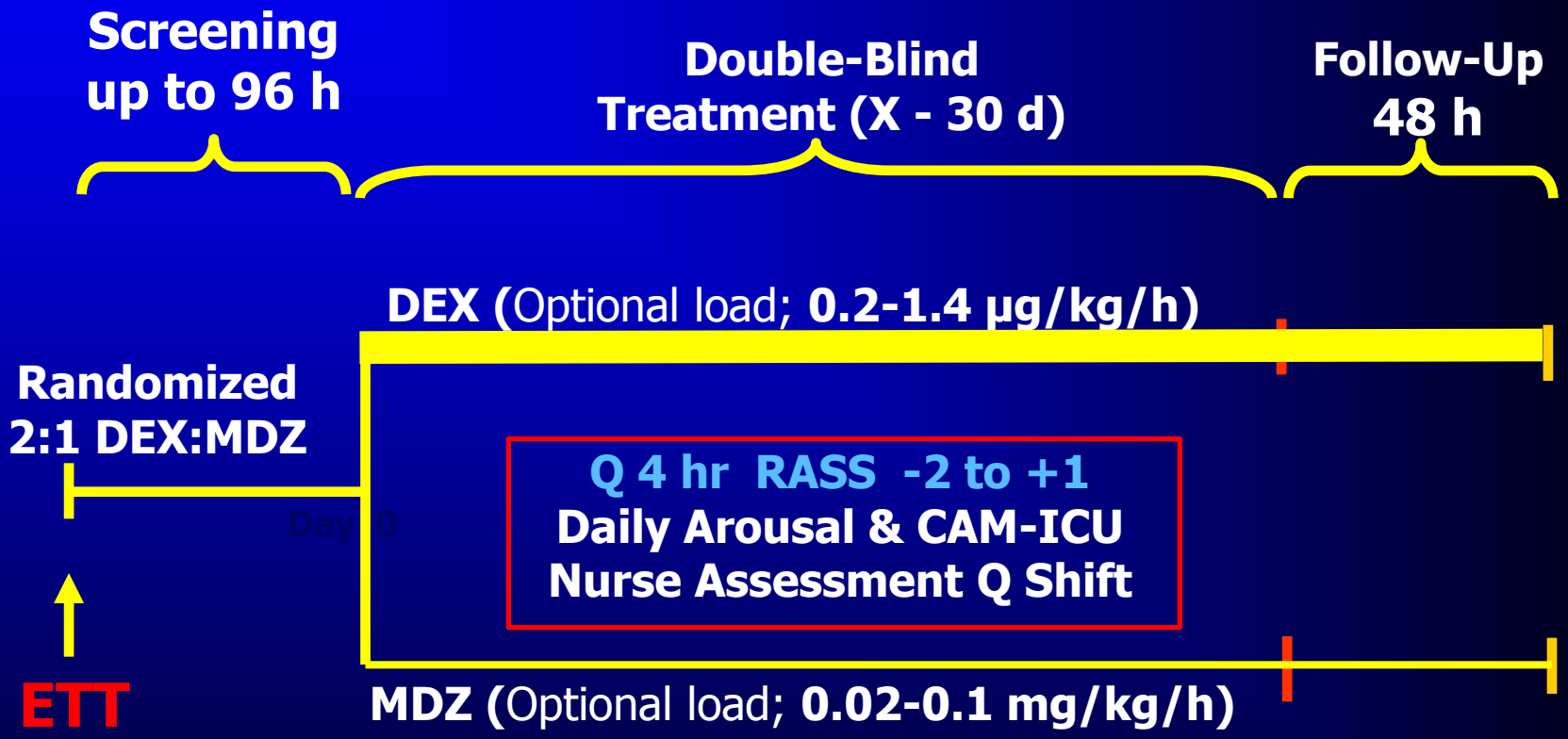
- Dex higher daily dose fentanyl 575 vs 150 mcg, p=0.006
- Drug effect vs Depth of Sedation effect

Pandharipande. JAMA 2007; 298:2644

Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients

A Randomized Trial



Riker. JAMA 2009; 301:489-99

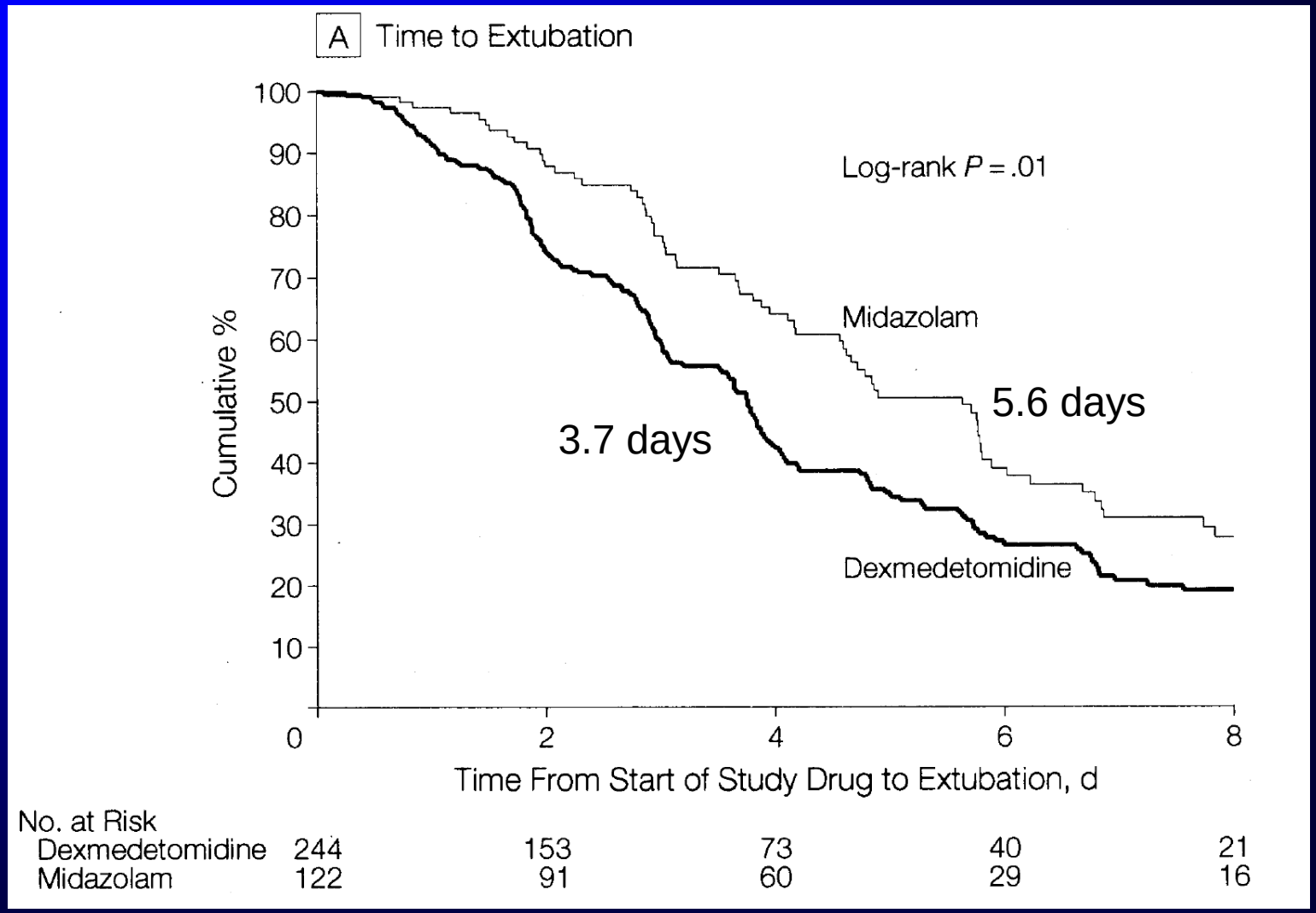
Time in Target Sedation Range

Dexmedetomidine	Midazolam	Diff	*P*
77.3%	75.1%	2.2%	0.18

- Same depth of sedation – similar time at light target in both groups
- Any differences in outcome NOT explained by deeper sedation in one group

Riker. JAMA 2009; 301:489-99

Time to Extubation: Kaplan-Meier



Riker. JAMA 2009; 301:489-99

Sedative vs Analgesic

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

The MENDS Randomized Controlled Trial

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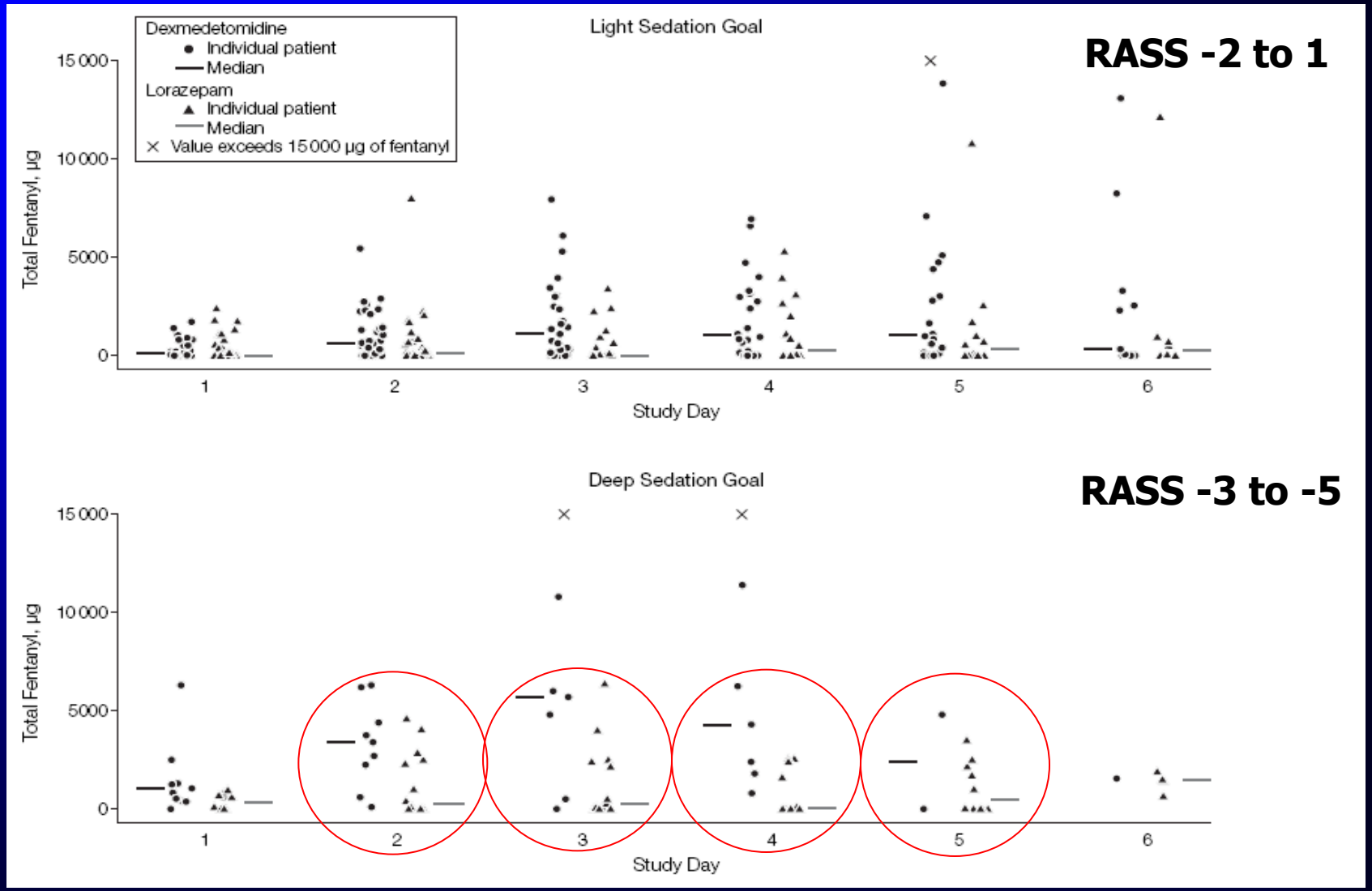
Sedative vs Analgesic



Pandharipande. JAMA 2007; 298:2644

Sedative vs Resources/Haloperidol

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

- RCT: Propofol/Midazolam vs “No Sedation”
- “No Sedation” = 1:1 nursing, sitter, PRN morphine, PRN haloperidol, continuous propofol for 6 hours x3, then continuous
  - 18% intervention protocol violation - continuous sedation
  - More agitated delirium (20% vs 7%, p=0.04), more haloperidol (p=0.014)
  - More ventilator-free days, shorter ICU/hospital LOS, mortality (0.06)
- Excluded 27 patients - died or extubated <48 hours - ???

Strom T. Lancet 2010; 375:475-80

Timing is Everything

Early Intensive Care Sedation Predicts Long-Term Mortality in Ventilated Critically Ill Patients

Yahya Shehabi[1,2], Rinaldo Bellomo[3,4,5,6], Michael C. Reade[7,8], Michael Bailey[5], Frances Bass[2], Belinda Howe[5], Colin McArthur[9], Ian M. Seppelt[10], Steve Webb[11,12], and Leonie Weisbrodt[13]; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group*

- SPICE
- Early deep sedation was defined by the number of times RASS assessments (collected every 4 h) were between 23 and 25 during the first 48 hours of ICU stay.
- Deep sedation was treated as a continuous variable. Early deep sedation was the primary exposure variable in the time-to-event analysis of outcomes occurring after 48 hours:
- time to extubation, time to subsequent delirium, time to hospital death, and 180-day mortality

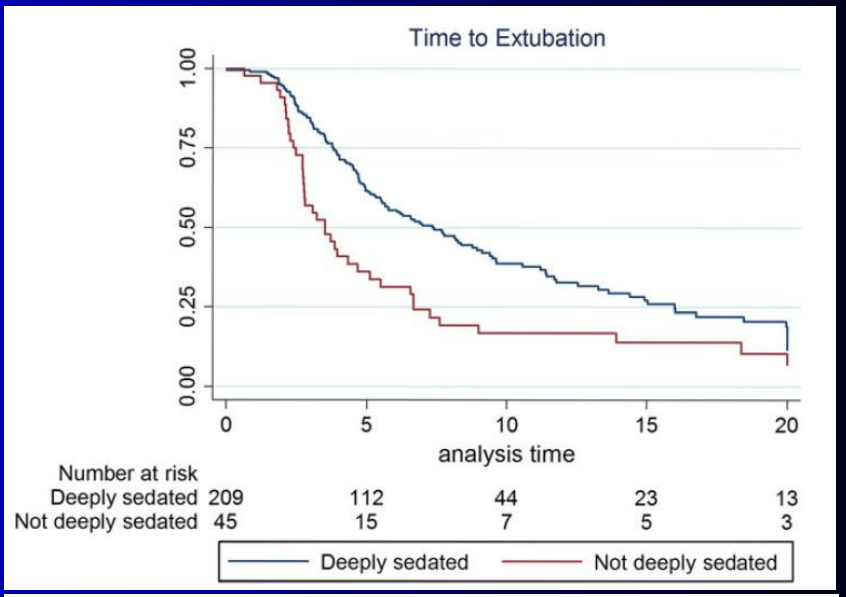
Shehabi. AJRCCM 2012; 186:724-31

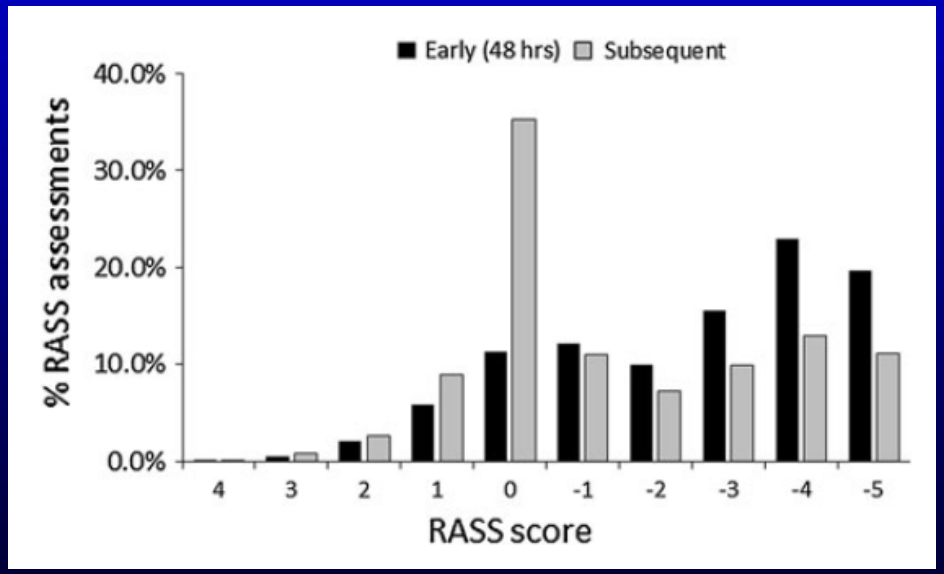
Timing is Everything

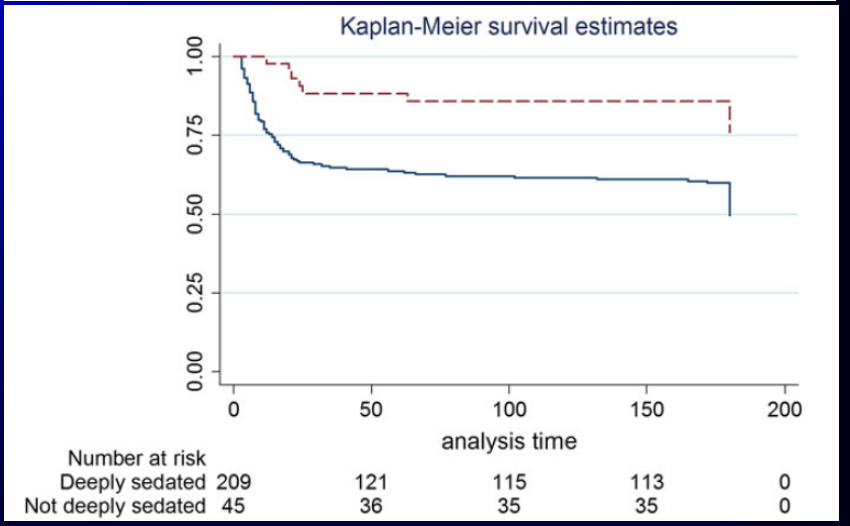
Yahya Shehabi
Lucy Chan
Suhaini Kadiman
Anita Alias
Wan Nasrudin Ismail
Mohd Ali T. Ismail Tan
Tien Meng Khoo

Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study

- SPICE







Shehabi. Intensive Care Med 2013; 39:910-18

Timing is Everything

Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial

*Gerald Chanques, Matthieu Conseil, Claire Roger, Jean-Michel Constantin, Albert Prades, Julie Carr, Laurent Muller, Boris Jung, Fouad Belafia, Moussa Cissé, Jean-Marc Delay, Audrey de Jong, Jean-Yves Lefrant, Emmanuel Futier, Grégoire Mercier, Nicolas Molinari, Samir Jaber, on behalf of the SOS-Ventilation study investigators**

- RCT - Interruption of sedation 2-4 hours after arrival ICU, PRN continuous sedation for 6 h. If >2 periods of sedation in 24 h, continuous sedation prolonged until next day
- Interruption group improved outcomes:
  - Shorter time to extubation (8 vs 50 hrs, $p<0.0001$)
  - Less coma (12% vs 50%, $p=0.006$)
  - Less delirium (43% vs 72%, $p=0.0004$)

Chanques G. Lancet Respir Med 2017; 5: 795–805

Possible Conclusions

- Control group is critical to understanding impact of intervention
- Targeted level of sedation may alter outcomes – light sedation probably the standard for many ICU patients (?deep)
- Protocol must prevent or monitor bail-out medications to avoid confounding
- Timing is everything – early (1st 48 hours) ICU sedation is important

Provocative Questions

- Can we take placebo-controlled ICU sedation studies off the table?
- Are we beyond time in target sedation zone as primary, or is this the Gold Standard for "Sedation"?
- Is mortality too high a bar?
- Does ICU sedation for 4-7 days impact late outcomes?
- Is resource utilization meaningful?
  - Ventilator duration or ventilator-free days
  - ICU LOS or ICU-free days
  - Discharge to home or rehab vs death/SNF
  - Short-term functional outcomes
  - Patient-focused priorities