Acetaminophen (Paracetamol) Can Prevent Delirium- Results from the DEXACET Trial

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HUMAN FIRST

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Disclosures

- Research funding
  - NHCAT, KL2TR002542

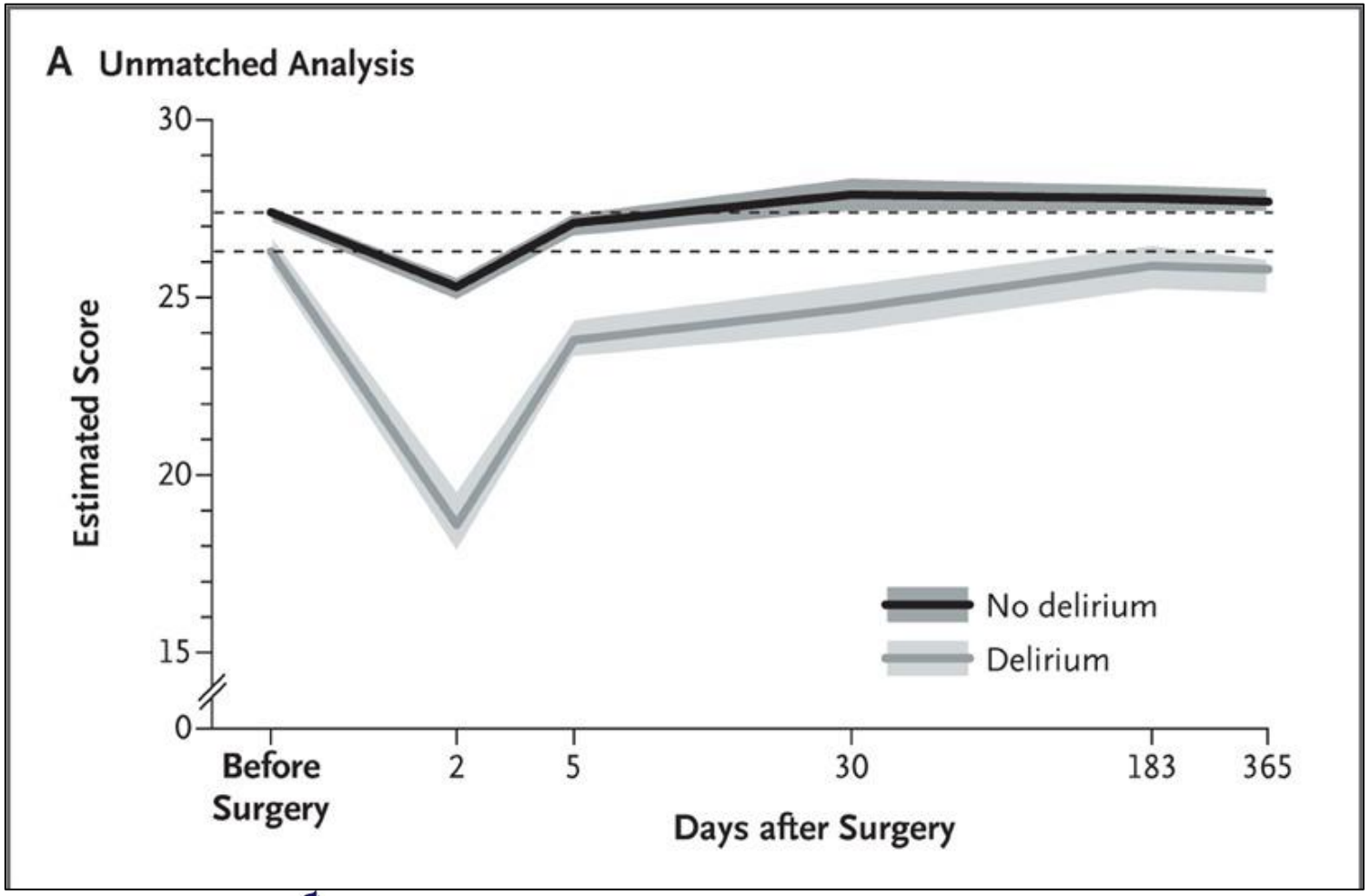
Post- Operative Delirium

- > 1/3 of inpatient surgeries in the US are performed on patients 65 years and older.
- These patients are vulnerable to post-operative delirium (POD).
  - Up to 50% in cardiac surgery
- POD is associated
  - increase in morbidity
  - Increased length of ICU stay
  - Increased hospital stay
  - Increased mortality
- Risk Factors
  - Age
  - Preexisting cognitive dysfunction
  - postoperative pain
  - use of opioids and sedatives

Int Psychogeriatr. 2004;16(2):175-193
J Gerontol A Biol Sci Med Sci. 2003;58(1):76-81.

Long Term Sequela of POD

Mini–Mental State Examination



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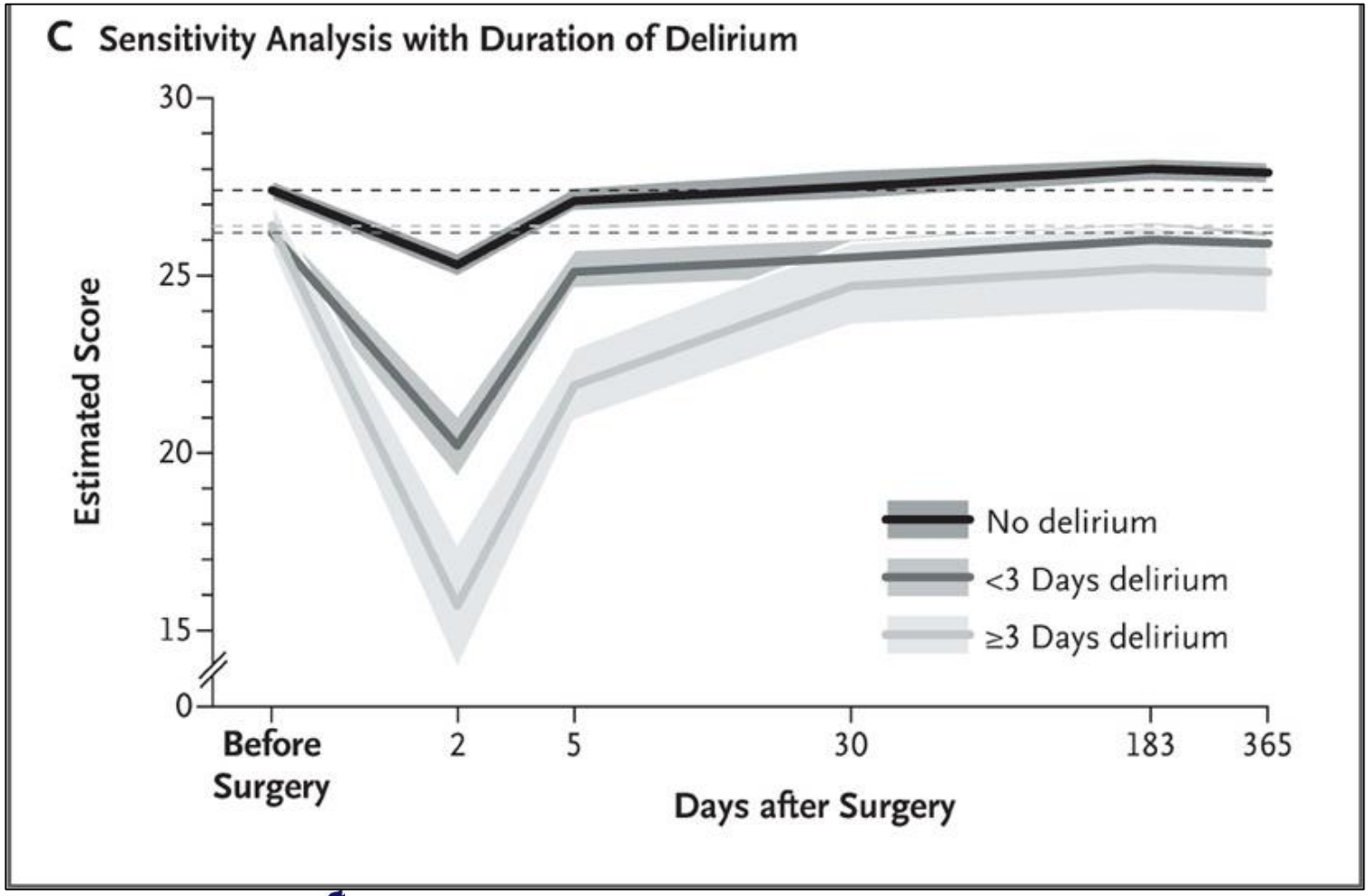
Saczynski , NEJM 2012

Long Term Sequela of POD

Mini–Mental State Examination



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Functional Decline after POD

Follow-up	With Delirium	Without Delirium	Adjusted Relative Risk *(95% Confidence Interval)*[$]
1 month	37/74 (50%)	28/105 (27%)	1.8 (1.2–2.6)
12 months	16/78 (21%)	11/100 (11%)	1.5 (0.6–3.3)

Functional decline is defined as a decline of ≥ 1instrumental activities of daily living (IADL) points at the follow-up assessment from the preoperative assessment.

Rudolf, *J Am Geriatr Soc.* 2010

POD Pharmacological Prevention Trials

Sources by Category	Setting/Sample Size *(n)*	Intervention	**Delirium Incidence (%)** *Intervention vs. Control, p-value*
Antipsychotics (Typical and Atypical)			
Fukata et al,[46] 2014	GI/Ortho surgery *(n=119)*	Haloperidol, IV	42 vs. 33, p =0.31
Hakim et al,[34] 2012	Cardiac surgery *(n=101)*	Risperidone, oral	4 vs. 34, p=0.03
Vochteloo et al,[47] 2011	Hip fracture surgery *(n=378)*	Haloperidol, oral	14 vs. 42, p<0.001
Wang et al,[48] 2012	Non-cardiac surgery *(n=457)*	Haloperidol, IV	15 vs. 23, p=0.03
Melatonin or Ramelteon			
Al-Aama et al,[49] 2011	Hospital, medical *(n=122)*	Melatonin, oral	4 vs. 19, p<0.02
de Jonghe et al, [50] 2014	Hip fracture surgery *(n=378)*	Melatonin, oral	30 vs. 26, p=0.40
Hatta et al,[51] 2014	Hospital, medical *(n=67)*	Ramelteon, oral	3 vs. 32, p=0.003
Perioperative Interventions			
Ashraf et al,[52] 2015	Cardiac catheterization *(n=93)*	Diphenhydramine and diazepam	0 vs. 0, p=NS
Lurati et al,[35] 2012	Non-cardiac surgery *(n=385)*	Sevoflurane	11 vs. 14, p=0.38
Stoppe et al, [53] 2013	Cardiac surgery *(n=30)*	Xenon	20 vs. 27, p=0.67
Whitlock et al,[53] 2015	Cardiac surgery *(n=7507)*	Methylprednisolone	8 vs. 8, p=0.80
Dighe et al,[54] 2014	Orthopedic surgery *(n=161)*	Gabapentin	12 vs. 9, p=0.53
Marcantonio et al,[37] 2011	Hip fracture surgery *(n=16)*	Donepezil, oral	64 vs. 64, p=0.94
Papadopoulos et al,[55] 2014	Orthopedic surgery *(n=106)*	Ondansetron, IV	35 vs. 53, p=0.07
Pesonen et al,[56] 2011	Cardiac surgery *(n=70)*	Pregabalin, oral	CAM-ICU, p=0.04

Abbreviations: GI = gastrointestinal; NS = not significant; IV = intravenous.

Pharmacological Prevention of POD

- Design and methodologic limitations include concerns
  - Delirium included those who had sub-syndromal delirium
  - Primary outcomes include measures other than delirium,
  - Delirium over time versus the incidence of delirium.
- The detrimental side effects of antipsychotic medications may preclude use
  - Haloperidol- extrapyramidal side effects.
  - Olanzapine and quetiapine- sedation.

Pharmacological Prevention of POD

- A recent Cochrane review showed no clear benefit of

The American Geriatrics Society Expert Panel on POD suggests that antipsychotics should be avoided for treatment of hypoactive delirium and their use be limited to the lowest effective dose for the shortest possible duration for severely agitated, distressed or self-threatening situations.

Rationale for Pain Control

- Delerium associated with uncontrolled pain
- Delerium associated with opiate use
- IV acetaminophen has been shown to reduce inflammation and may confer central analgesic properties
- Acetaminophen may decrease opioid consumption in both opioid-naive and exposed patients.

Am J Ther. 2005;12(1):46-55.
Front Public Health. 2013;1:25.

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery

The DEXACET Randomized Clinical Trial

Balachundhar Subramaniam, MD, MPH; Puja Shankar, MD; Shahzad Shaefi, MD, MPH; Ariel Mueller, MA; Brian O'Gara, MD; Valerie Banner-Goodspeed, MPH; Jackie Gallagher, MS; Doris Gasangwa, BS; Melissa Patxot, BS; Senthil Packiasabapathy, MBBS; Pooja Mathur, BS; Matthias Eikermann, MD, PhD; Daniel Talmor, MD, MPH; Edward R. Marcantonio, MD, SM

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JAMA 2019

Trial Design

- 60 years or older undergoing CABG
- 2 X 2 Factorial Design
  - Propofol vs Dexmedatomidine
  - Acetaminophen vs Placebo
- Four combinations (1:1:1:1) of analgesics and sedatives
  - Acetaminophen and dexmedetomidine
  - Acetaminophen and propofol
  - Dexmedetomidine and placebo
  - Propofol and placebo.

Exclusions

- Preoperative left ventricular ejection fraction <30%
- Pre-existing cognitive impairment, Alzheimer's disease, Parkinson's disease or medications for cognitive decline
- History of recent seizures
- Serum creatinine >2 mg/dL
- Liver dysfunction
- Recent alcohol abuse
- English language limitations
- Hypersensitivity to study medications
- Emergent surgery

Dosing

- Acetaminophen (or Placebo)
  - 1 gr every 6 hours for total of 8 doses.
- Dexmedetomidine
  - Bolus dose of 0.5 to 1 mcg/kg IV during chest closure
  - Maintenance infusion of 0.1 to 1.4 mcg/kg/hour
- Propofol group
  - Bolus during chest closure
  - Maintenance dose of 20 to 100 mcg/kg/min

Primary Outcome

- Confusion Assessment Method (CAM) or CAM-ICU for intubated patients
  - Acute onset and fluctuating course
  - Inattention
  - Disorganized thinking
  - Altered level of consciousness

Secondary Outcomes

- Duration of delirium,
- Postoperative cognition at discharge
  - MoCA (range 0 [worst] to 30 [best])
- 48-hour breakthrough analgesic requirements
  - (fentanyl dose * 2.4) + (hydromorphone dose * 4) + morphine dose + (oxycodone dose * 1.5)
- ICU and hospital lengths of stay.

Figure 1. Participant Flow in the DEXACET Randomized Clinical Trial

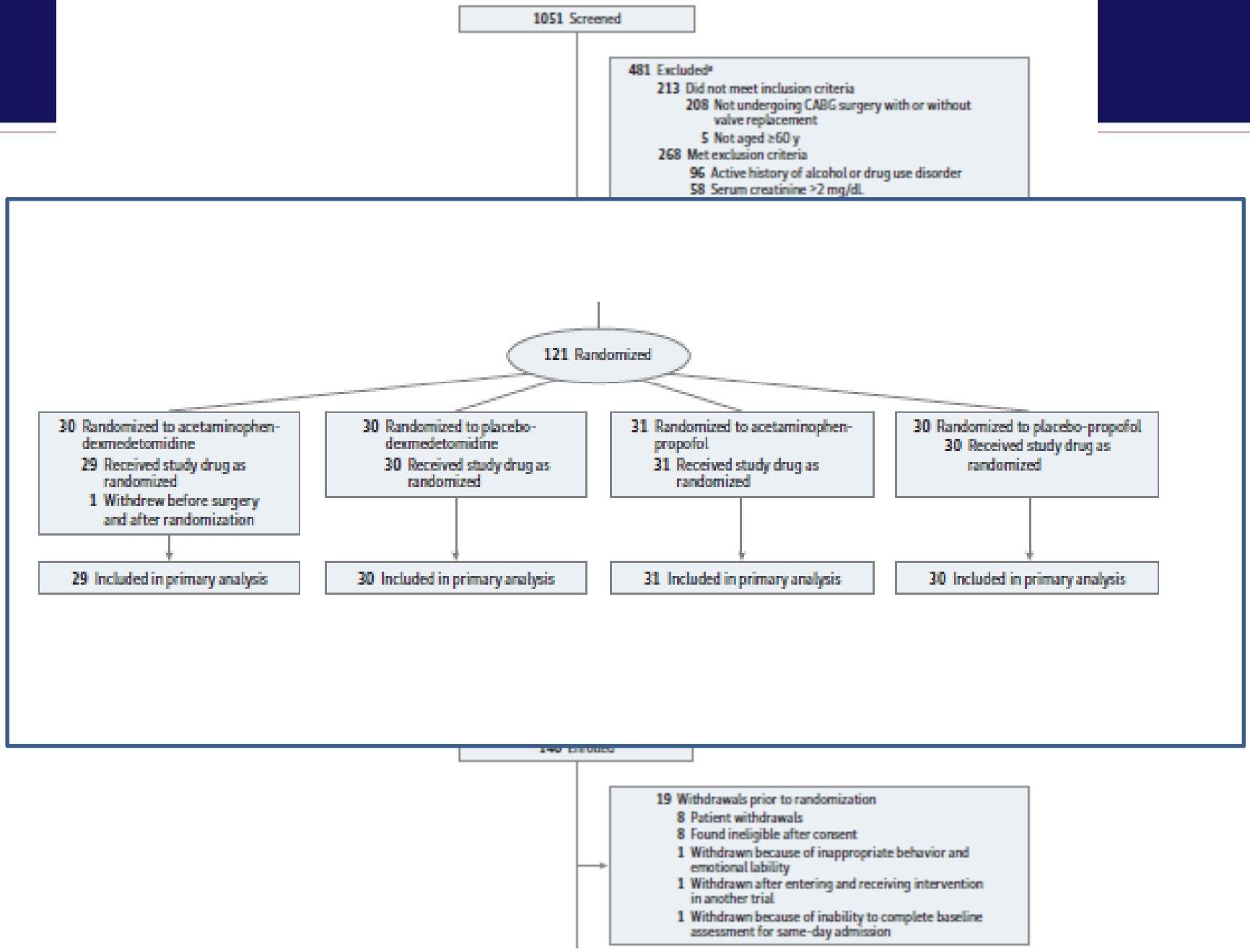


Table 1. Baseline Characteristics of Study Participants by Treatment Group

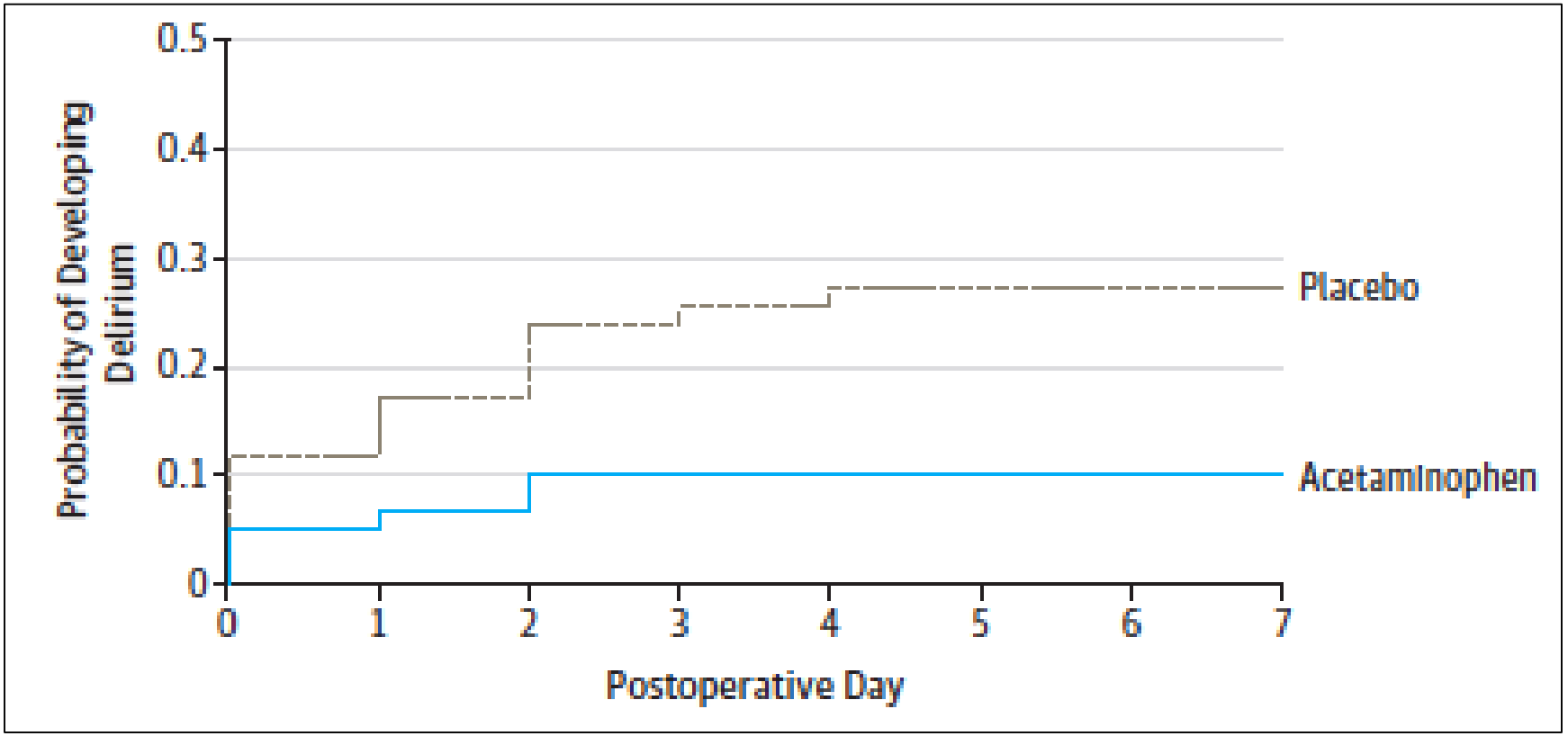
Characteristics	Acetaminophen-Dexmedetomidine (n = 29)	Placebo-Dexmedetomidine (n = 30)	Acetaminophen-Propofol (n = 31)	Placebo-Propofol (n = 30)
Demographics				
Sex, No. (%)				
Male	26 (89.7)	25 (83.3)	24 (77.4)	26 (86.7)
Female	3 (10.3)	5 (16.7)	7 (22.6)	4 (13.3)
Age, median (IQR), y	64 (63-72)	69 (63-74)	70 (66-75)	71 (64-79)
Patient-reported race, No. (%)[a]				
White	26 (89.7)	28 (93.3)	29 (93.6)	28 (93.3)
Black/African American	2 (6.9)	1 (3.3)	1 (3.2)	1 (3.3)
Asian	0	0	1 (3.2)	0
Multiracial	0	0	0	1 (3.3)
Other	0	1 (3.3)	0	0
Unknown/not specified	1 (3.5)	0	0	0
Hispanic or Latino, No. (%)	1 (3.5)	1 (3.3)	0	2 (6.7)
Weight, median (IQR), kg	89.1 (80.4-102.0)	87.6 (82.0-102.0)	84.1 (79.0-93.2)	90.0 (75.8-107.0)
Height, median (IQR), cm	173.0 (167.6-180.3)	172.7 (167.6-178.0)	170.2 (167.6-173.3)	175.1 (167.6-180.0)
Body mass index, median (IQR)[b]	29.7 (26.6-32.3)	29.4 (27.0-32.0)	28.5 (26.6-32.3)	29.2 (25.9-34.3)
Surgical characteristics				
Procedure, No. (%)				
Isolated CABG surgery	19 (65.5)	18 (60.0)	19 (61.3)	23 (76.7)
CABG surgery + mitral valve replacement	1 (3.5)	0	1 (3.2)	0
CABG surgery + aortic valve replacement	8 (27.6)	8 (26.7)	10 (32.3)	6 (20.0)
Other[c]	1 (3.5)	4 (13.3)	1 (3.2)	1 (3.3)
No. of arteries affected, median (IQR)	3 (2-4)	3 (2-3)	3 (2-3)	3 (2-3)
Preoperative statin use, No. (%)	24 (82.8)	25 (83.3)	29 (93.6)	27 (90.0)
Cross-clamp time, median (IQR), min	67 (58-84)	73 (60-93)	78 (66-87)	64 (54-96)

Outcomes

Table 2. Primary and Secondary Outcomes

Outcomes	Analgesic				Sedative			
	Acetaminophen (n = 60)	Placebo (n = 60)	Difference (95% CI)	*P* Value	Dexmedetomidine (n = 59)	Propofol (n = 61)	Difference (95% CI)	*P* Value
Delirium								
In-hospital delirium (primary outcome), No. (%)	6 (10.00)	17 (28.33)	−18.3% (−32.0% to −4.6%)	.01	10 (16.95)	13 (21.31)	−4% (−18% to 10%)	.54
Days with delirium, median (IQR)	1.0 (1.0 to 1.0)	2.0 (1.0 to 3.0)	−1 (−2 to 0)	.03	1.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	−1 (−2 to 0)	.31
Worst delirium severity, median (IQR)[a]	9.0 (7.0 to 11.0)	8.0 (6.0 to 11.0)	1.0 (−2.0 to 3.0)	.81	6.5 (6.0 to 11.0)	9.0 (8.0 to 11.0)	−2.5 (−3.0 to 2.0)	.39
MoCA score[b]								
Baseline, median (IQR)	24.0 (22.0 to 26.0)	23.5 (20.4 to 26.0)	0.5 (−1 to 2)	.39	24.0 (21.0 to 26.0)	24.0 (21.0 to 26.0)	0 (−1 to 1)	.84
Discharge, median (IQR)	24.0 (21.0 to 26.0)	24.0 (20.0 to 26.0)	0 (−1 to 2)	.29	24.0 (21.0 to 25.0)	24.0 (21.0 to 26.0)	0 (−2 to 1)	.55
Change from baseline, median (IQR)	0.0 (−2.0 to 1.0)	−0.4 (−2.0 to 1.0)	0.4 (−1.0 to 1.0)	.82	0.0 (−1.6 to 1.0)	−0.9 (−2.0 to 1.2)	0.9 (−1.0 to 1.0)	.82
Time-related outcomes								
Hospital length of stay, median (IQR), d	8.0 (6.0 to 9.5)	8.5 (6.0 to 11.0)	−0.5 (−2 to 0)	.13	8.0 (6.0 to 10.0)	8.0 (6.0 to 11.0)	0 (−1 to 1)	.71
ICU length of stay, median (IQR), h	29.46 (25.07 to 49.43)	46.17 (27.83 to 81.44)	−16.7 (−20.3 to −0.8)	.02	31.98 (27.42 to 54.27)	29.70 (25.65 to 56.55)	2.3 (−3.2 to 5.0)	.66
48-h Postoperative medication administration								
Total morphine equivalent administered, median (IQR), μg[c]	322.5 (233.0 to 450.0)	405.3 (306.5 to 590.3)	−83 (−154 to −14)	.02	328.8 (232.5 to 435.0)	397.5 (292.5 to 573.0)	−69 (−155 to −4)	.04

Time to Delirium



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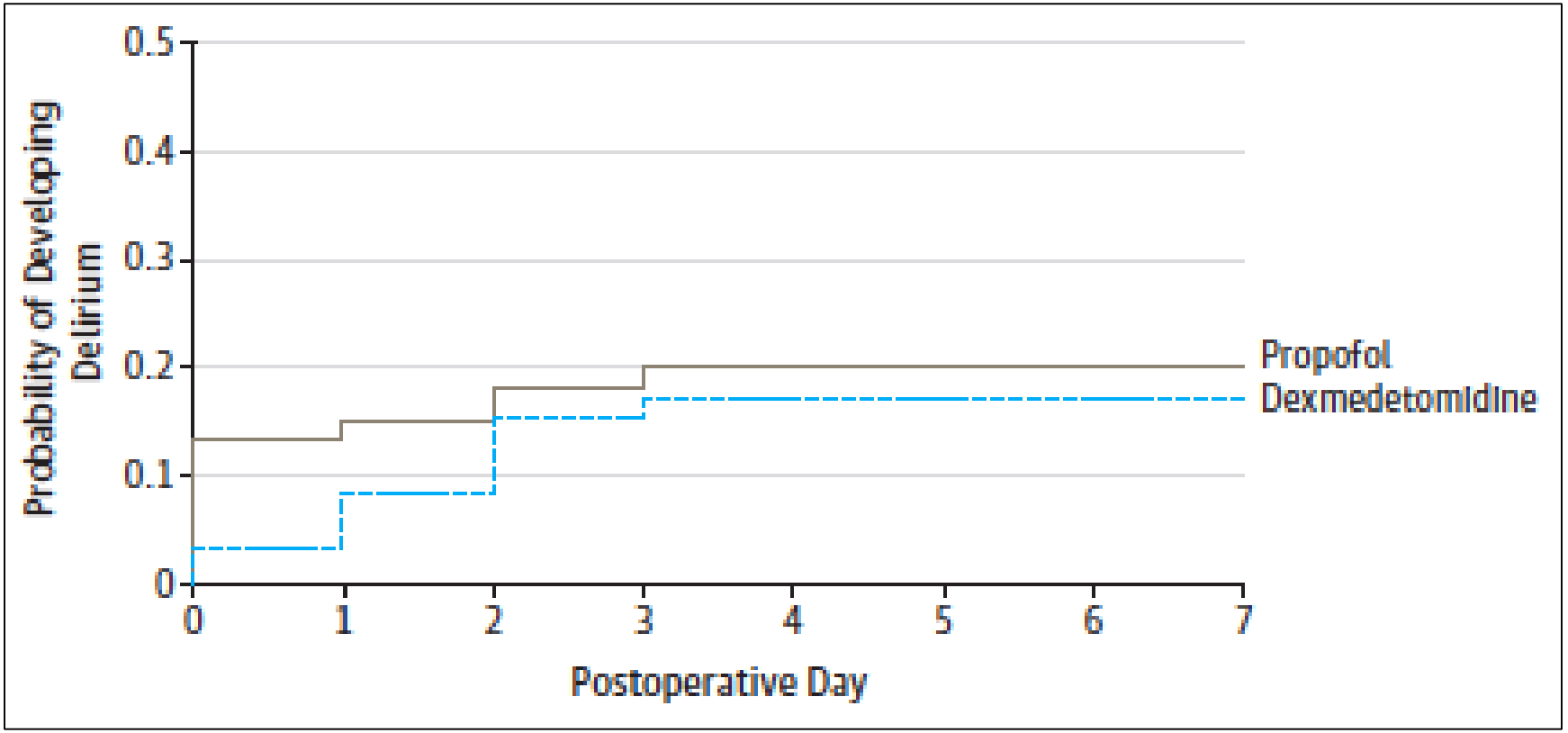

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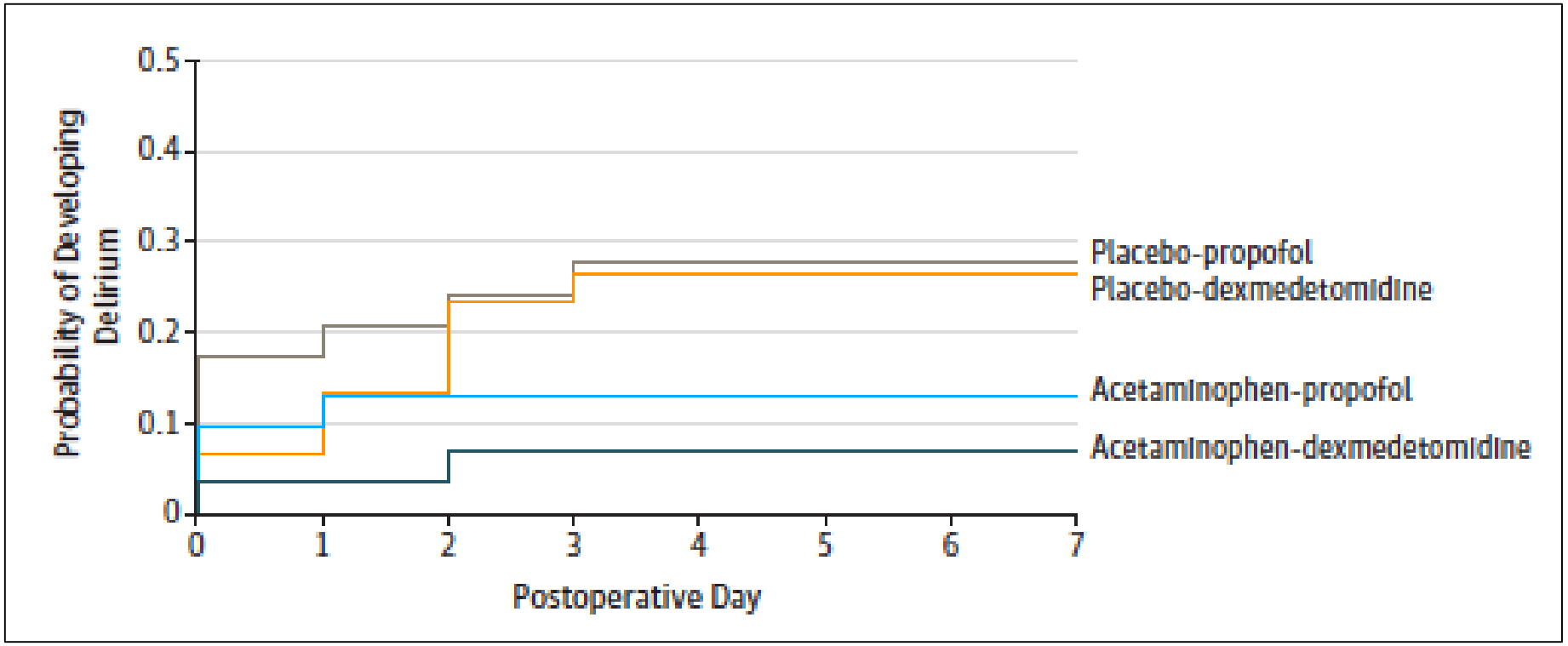

Table 3. Secondary Outcomes Stratified by Factorial Group[a]

Outcomes	Acetaminophen-Dexmedetomidine (n = 29)	Placebo-Dexmedetomidine (n = 30)	Acetaminophen-Propofol (n = 31)	Propofol-Placebo (n = 30)	*P* Value
Delirium					
In-hospital delirium No. (%)	2 (6.9)	8 (26.7)	4 (12.9)	9 (30.0)	.07
Days with delirium, median (IQR)	1 (1 to 1)	1 (1 to 3)	1 (1 to 1)	3 (2 to 3)	.047
Worst delirium severity, median (IQR)[b]	10 (9 to 11)	6 (6 to 9)	8 (6 to 10)	9 (8 to 11)	.35
MoCA score[c]					
Baseline, median (IQR)	23 (22 to 26)	24 (20 to 26)	24 (22 to 26)	23 (21 to 26)	.85
Discharge, median (IQR)	24 (21 to 25)	24 (20 to 26)	25 (22 to 27)	24 (21 to 25)	.49
Change from baseline, median (IQR)	0.0 (−1.1 to 1.0)	0.0 (−1.8 to 1.3)	0.5 (−2.5 to 2.0)	−1.0 (−2.0 to 1.0)	.93
Time-related outcomes					
Hospital length of stay, median (IQR), d	8 (6 to 9)	9 (7 to 11)	8 (6 to 11)	8 (6 to 11)	.37
ICU length of stay, median (IQR), h	28.8 (24.9 to 43.5)	49.1 (29.0 to 92.9)	30.3 (25.3 to 52.8)	29.3 (25.7 to 74.3)	.02
48-h Postoperative medication administration					
Total morphine equivalent administered, median (IQR), μg[d]	304 (214 to 376)	391 (272 to 540)	360 (270 to 541)	416 (332 to 630)	.02

Why May This Work- Pain Relief and Opioid Sparing?

- Undertreated pain has been found to be an independent risk factor for delirium
  - Lynch, Anesth Analg 1998
- Increases the risk of delirium by nine times compared to those patients who are adequately treated.
  - Morrison, J Gerontol A Biol Sci Med Sci. 2003
- Systemic opioids may lead to delirium:
  - Nausea and vomiting
  - Sedation
  - Decreased bowel activity
  - Urinary retention
  - Respiratory depression

Why May This Work- Inflammation?

- Acetaminophen readily crosses the blood-brain barrier and inhibits cyclooxygenase
  - Ghanem, Pharmacol Res. 2016
- Has central anti-inflammatory and antioxidant effects
  - Tripathy, J Neuroinflammation. 2009
- Acetaminophen has been found to protect hippocampal and dopaminergic neurons from oxidative stress and blunt neuronal apoptosis
  - Bisaglia, Neurochem Int. 2002
- Extensive research has demonstrated an association between neuroinflammation and degenerative neural disorders.
  - Skapia, Ann N Y Acad Sci. 2007

Putting it Together

- Neuro-inflammation during the perioperative period has been found to be associated with POD
- Acetaminophen
  - Reduces inflammation
  - Treats pain
  - Reduces opiate consumption

Conclusions

- POD is a major problem
- IV Acetaminophen is a safe and effective pain medication
- It may reduce the incidence of POD.
- Larger study needed
  - IV vs PO?
  - Role for Dex?
  - Length of dosing?
  - Other ICU populations?
  - Include patients with baseline dementia or other cognitive impairment?

The Team

- Balachundhar Subramaniam
- Puja Shankar
- Shahzad Shaefi
- Ariel Mueller
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- Jackie Gallagher
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