## Title

Cardiac surgery, ICU sedation, and delirium: is dexmedetomidine the silver bullet?



## Journal

Current Opinion in Anaesthesiology, 36(1)

## ISSN

0952-7907

## Authors

Smith, Wendy
Whitlock, Elizabeth L

## Publication Date

2023-02-01

## DOI

10.1097/aco.0000000000001207

Peer reviewed

HHS Public Access

Author manuscript

*Curr Opin Anaesthesiol*. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

*Curr Opin Anaesthesiol*. 2023 February 01; 36(1): 50–56. doi:10.1097/ACO.0000000000001207.

# Cardiac surgery, ICU sedation, and delirium: is dexmedetomidine the silver bullet?

**Wendy Smith, MD**[1], **Elizabeth L Whitlock, MD, MSc**[1,*]

[1]Department of Anesthesia & Perioperative Care, University of California, San Francisco, San Francisco, CA

## Abstract

**Purpose of review:** Delirium is a marker of acute brain insufficiency and a harbinger of poor outcomes and increased healthcare costs. Despite success preventing delirium by non-pharmacologic measures, the incidence in the post-cardiac surgical ICU population remains high. Dexmedetomidine, a selective alpha-2 agonist, is a plausible preventive agent with sedative, anxiolytic, analgesic, sympatholytic and anti-inflammatory properties, and is the subject of very active study in cardiac surgery populations.

**Recent findings:** Recent trials, including DEXACET (2019), DECADE (2020), LOWDEXDEL (2021), and DIRECT (2022) individually, failed to show a benefit for dexmedetomidine and highlighted associated risks. Meta-analyses have offered conflicting results, highlighting the complexity of delirium, and likely interaction of multiple etiological pathways; those that concluded benefit often were driven by trials at high risk of bias. Meta-analyses excluding biased trials currently suggest no benefit for dexmedetomidine over control in unselected cardiac surgical populations.

**Summary:** While using dexmedetomidine to prevent delirium in unselected cardiac surgical patients is not supported by current evidence, there remains hope that it may offer benefits in highly selected populations, and further trials are ongoing.

### Keywords

Dexmedetomidine; Cardiac surgery; Postoperative delirium

## Introduction

Delirium lies at the intersection of traditional and patient-centered outcomes, as it directly leads to personal and family distress, and it is reproducibly associated with delayed neurocognitive recovery, loss of independence and increased likelihood of non-home discharge, increased hospital length of stay, cost, morbidity and mortality.(1,2) According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, delirium is defined

*Corresponding author: Elizabeth L Whitlock, 521 Parnassus Ave, 4th Floor, Campus Box 0648, San Francisco, CA 94143, Elizabeth.whitlock@ucsf.edu, 415-514-3755.

Conflicts of interest:
Neither author has any potential conflict of interest to disclose.

as a disturbance in attention, representing a change from baseline, which develops over a short period of time, fluctuates over the course of the day, is accompanied by an additional cognitive deficit, is not better explained by a pre-existing neurocognitive condition and is a direct consequence of a physiologic insult.(3) In the postoperative period, delirium can be difficult to diagnose, though it is vital to do so as it is an indicator of brain insufficiency and a harbinger of worsened outcomes.

While all patients undergoing surgical procedures are at some risk of developing post-operative delirium (POD), those undergoing cardiac surgery are at particular risk due to the nature of their underlying disease processes and the inflammatory milieu generated by the particular physiologic stresses encountered in the cardiac operating room.(4) Given the implications of delirium from a patient-centered, traditional outcome and cost perspective, it is a prime target for preventive and treatment measures. Based on data from the critical care, non-cardiac surgical population and some preliminary data in cardiac patients, there was tremendous initial enthusiasm about the role dexmedetomidine might play in the fight against delirium. As the data evolve, unfortunately, the answer remains unclear. Here, we review recent evidence for the potential of, and the areas of disappointed hopes for, the use of dexmedetomidine in post-cardiac surgical and ICU delirium. (5,6)

## Dexmedetomidine as a defense against delirium

Dexmedetomidine is a selective alpha-2 adrenergic agonist with sedative, anxiolytic, analgesic, sympatholytic and anti-inflammatory properties. In theory, it has the potential to mitigate the effects of delirium in several ways (Table 1). First, dexmedetomidine may indirectly limit the use of other deliriogenic drugs such as benzodiazepines, propofol, and opiates. However, its direct actions are plausibly protective as well. Via sympatholysis of pre- and post-synaptic alpha-2 receptors at the locus coeruleus, dexmedetomidine sedation is itself more consistent with natural sleep, potentially decreasing delirium risk via physiologic sleep promotion. (10) More recently, a role in protection against ischemia-reperfusion injury, through anti-inflammatory pathways, has been suggested. (11) The direct sympatholytic effects of dexmedetomidine may decrease risk for major adverse cardiac events in other postoperative populations, conceivably sparing delirium events indirectly. It is no surprise, given these properties and evidence to support a reduction in delirium incidence in preliminary studies that dexmedetomidine would be viewed with tremendous enthusiasm in the cardiac surgical population. Despite extensive investigation over the last decade, however, the role of dexmedetomidine in these patients remains murky.

## What do the data say? It depends on how you look at it.

As knowledge of the insidious and far-reaching implications of delirium has evolved, the search for an effective prevention and/or treatment strategy has accelerated. Promising randomized trial data showing decreased rates of delirium and time to extubation in patients treated with dexmedetomidine, compared to traditional sedatives from the ICU literature, prompted interest in applying this drug's unique properties to target other vulnerable patient populations. (12,13) Initially, several small RCTs were conducted in cardiac surgical patients, with highly heterogeneous methodology (e.g., blinding; outcomes;

dosing regimens) that made them difficult to interpret. A formal meta-analysis with trial sequential analysis, which focused on the narrower application of post-cardiac surgery sedation with dexmedetomidine compared with propofol, found evidence for lower delirium risk and earlier extubation times in trials published between 2005 and 2016, but at the expense of a 3-fold increase in bradycardia. (14) This finding offered additional justification for larger, more rigorous RCTs in this population.

More recent trials – for example, DEXACET (2019), DECADE (2020), LOWDEXDEL (2021), and DIRECT (2022), among others (Table 2) – have contributed additional evidence. Unfortunately, questions remain. DEXACET used a factorial randomization scheme in n=120 patients to test the impact of intravenous acetaminophen and dexmedetomidine on delirium; while acetaminophen was effective, dexmedetomidine – started at chest closure with a 0.5-1ug/kg bolus and an infusion of 0.1-0.4ug/kg/hr – was not, although the confidence interval was wide.(21) LOWDEXDEL used a similar infusion strategy, beginning at chest closure and run at 0.4ug/kg/hr, in n=349 patients and also demonstrated no benefit in delirium incidence compared to propofol. (22) The DIRECT trial, which randomized n=70 adults aged 75 and older, found no benefit for open-label dexmedetomidine in their primary outcome of quality of recovery at postoperative day 3; delirium incidence, which was a secondary outcome, was found to be qualitatively lower in the dexmedetomidine group (24% vs 42%), but with a nonsignificant p-value due to lack of study power.(2) These small additional trials, among others, have been criticized for lack of blinding, low study power, and poor generalizability, but in total fail to provide strong support for the use of dexmedetomidine in a cardiac surgical population to prevent delirium.

In contrast, the large (n=798) DECADE trial was a randomized, placebo-controlled study across six academic medical centers comparing intraoperative and postoperative dexmedetomidine vs. placebo and evaluating for co-primary outcomes of new onset atrial fibrillation and delirium. Surprisingly, given meta-analytic evidence to the contrary, no statistically significant difference was seen in the incidence of delirium between the groups, and the trend was indeed towards a *higher* incidence of delirium in the dexmedetomidine group (relative risk 1.48 [0.99-2.23]) which nearly achieved statistical significance. Recruitment was stopped early for futility, with the atrial arrhythmia coprimary outcome providing strong evidence for lack of benefit. Further, there was a high incidence of clinically significant hypotension in the dexmedetomidine group, despite use of a low-dose regimen ranging from 0.1ug/kg/hr (before and during bypass) to 0.4ug/kg/hr (in ICU). (19) DECADE's disappointing conclusion was that dexmedetomidine should not be used to reduce risk of atrial arrhythmias or delirium.

## Meta-analysis: trials and tribulations

As heterogeneous trials accumulate heterogeneous conclusions, perhaps meta-analysis – formally considering, in summary, the total of the extant evidence – can provide illumination. Indeed, several meta-analyses have been published on this topic in recent years. (Table 3). An updated meta-analysis by Li and colleagues, which searched through August 2020 and incorporated DECADE and DEXACET, found strong summary evidence for dexmedetomidine's role in reducing delirium after cardiac surgery (23). This meta-

analysis attempted to separate effective and ineffective trials by performing several subgroup analyses, recognizing that the substantial heterogeneity in population and dose created unfortunate complexity to the message for clinicians. In subgroup analysis, the authors showed that benefit from dexmedetomidine was more likely to be found in studies which included younger patients (rather than limiting exclusively to older adults). They also demonstrated that initiating use of dexmedetomidine intraoperatively, then continuing it postoperatively, was more likely to be *ineffective* compared with postoperative-only administration. This was, interestingly, consistent with Duan's meta-analysis of cardiac and non-cardiac surgical patients.(25) Counterintuitively, then, dexmedetomidine exposure for *shorter* duration and in *less vulnerable* patients seems to be most likely to be effective at preventing delirium after cardiac surgery. Could the commonly seen hypotension in patients receiving longer durations of dexmedetomidine be, itself, causing delirium, which obscures a weakly protective effect in those most vulnerable to hypoperfusion (e.g., older adults) and is exacerbated by longer durations of infusion? This seems unlikely; a post-hoc analysis of the DECADE trial failed to show an association between intraoperative hypotension and delirium.(26) Thus, the possibility remains that these counterintuitive conclusions suggest a deeper problem with the underlying literature.

Though the results from Li et al seemed encouraging for a somewhat peculiar subset of patients, an updated meta-analysis helps provide clarity between those two potential explanatory hypotheses. Analyzing many of the same studies in a literature search through April 2021, Patel and colleagues found a statistically significant decrease in POD when considering all studies - but, problematically, this vanished once studies with high concerns for bias were eliminated from the analysis.(24). This is consistent with other areas of medical literature, in which initial small exploratory trials promoted enthusiasm, but larger and more rigorous trials in broad populations have failed to replicate the benefits. Meta-analysis is only as strong as the methdology of the underlying material, and as less-biased material (i.e., well-conducted, blinded randomized trials) accumulates, meta-analytic conclusions in this area are trending towards *lack* of benefit. Thus, based on the best available evidence, dexmedetomidine should not be uncritically used to prevent postoperative delirium in cardiac surgical patients.

## A more targeted approach: ongoing studies

However, it is premature to suggest that dexmedetomidine cannot offer delirium benefit in any cardiac surgical population. Given these patients' multifaceted risk profiles, combined with multiple aberrant stress responses in a complex physiologic milieu, and considering the tremendous potential variability in dosing strategy, it may not be surprising that previous studies have failed to yield a definitive answer. Tables 2 & 3 list a sampling of studies highlighting differences in populations, timing, and dosage of dexmedetomidine and research methodology that has led to a high degree of heterogeneity and has made a generalized interpretation challenging. Based on previous work, optimism around identifying a particular population and dosing regimen at highest likelihood of benefit has set the groundwork for ongoing studies.

ALPHA2PREVENT and EXACTUM are two multi-center, double-blinded, placebo-controlled RCTs, currently underway, which are looking at more specific subsets of the cardiac surgical patient population and more specific components of POD. (27,28) ALPHA2PREVENT will enroll 900 patients in a 1:1:1 ratio to receive dexmedetomidine, clonidine or placebo at a fixed dose regimen from the start of cardiopulmonary bypass, continuing for at least 12 hours up until discharge from the ICU. The promise of this study lies in their pre-operative assessment of cognitive function and frailty, limiting inclusion to patients who are at least 70 years of age and have concomitant measurements of implicated inflammatory markers, to biochemically identify a population more likely to benefit. EXACTUM is targeting the question of dexmedetomidine promotion of physiologic sleep/wake cycles in the prevention of POD. 348 patients will be enrolled and randomized to nocturnal (20:00 – 08:00) dexmedetomidine or placebo, starting POD 0 and continuing through ICU stay. Baseline cognitive function and sleep habits will be recorded, and, reflecting best evidence for nonpharmacologic delirium prevention, standard anti-delirium pathways will be followed regardless of group assignment to offer true comparison with standard-of-care.(29)

## Is there still a role for observational analyses?

While there is now fairly robust short-term randomized trial data demonstrating that use of dexmedetomidine in unselected cardiac surgery patients is unwise, long-term outcomes have been understudied. A relevant recent example of an observational study used causal inference techniques – propensity score analysis and inverse probability of treatment weighting – to look at 5-year survival in cardiac surgical patients who did, versus did not, receive dexmedetomidine.(30) Understanding the findings of this study, and the limitations of the methodology, may help readers interpret observational literature on dexmedetomidine.

In this single-center retrospective study, dexmedetomidine was used at the discretion of the attending anesthesiologist. The authors created a propensity score, which calculates the probability of receiving dexmedetomidine based on measured factors. Dexmedetomidine was used more often in patients with isolated valve surgery, and used less often in those with coronary artery disease, renal failure, myocardial infarction, urgent surgery, and longer cardiopulmonary bypass and aortic cross clamp times. They then used the propensity score to adjust for differences in who received dexmedetomidine and create a “pseudo randomized trial” population of people with equal probability of receiving dexmedetomidine who, in real life, either did or not receive it. No matter how good the propensity match was – and the authors showed that observed differences were reasonably well accounted for – the primary finding that dexmedetomidine use was associated with an absolute risk reduction in 5-year mortality of 7%, is provocative, but is almost certainly an overestimate because of limitations which are common to *nearly all* observational studies of dexmedetomidine in cardiac surgical patients. Namely, residual confounding nearly always exists, since only measured covariates can be adjusted for.

The non-dexmedetomidine group had substantial evidence of being, at baseline, higher-risk, which is often under-addressed by adjustment for binary (yes/no) factors, as was done here. For example, if one adjusts for “coronary artery disease,” which occurs on a spectrum of

severity, people who have “no” coronary artery disease have a range from zero to subclinical significant disease, and those who “have” coronary artery disease range from minimal and clinically insignificant, but diagnosed, disease through a nearly nonfunctional coronary circulation. These hidden differences are not balanced by propensity score methodology, so heterogeneity within broad categories may lead to unmeasured confounding. Another example is that the methodology allowed dexmedetomidine-receiving valve replacement patients to be matched with non-dexmedetomidine multivessel coronary artery bypass graft patients, which may not control effectively for long-term risk of death. Further, dexmedetomidine was used at anesthesiologist discretion; were anesthesiologists who used dexmedetomidine also adopters of other potentially beneficial strategies – cerebral oximetry, tighter blood pressure control, careful blood glucose management? If one hypothesizes that anesthesiologists who used dexmedetomidine were “better” – in unmeasured, and therefore unadjusted-for, ways – then perhaps a “good” anesthesiologist explains the 7% absolute reduction in mortality with dexmedetomidine. There is no way for this study to refute that (bold, and overly simplistic) counterexplanation. A tweet and image from Martin Halla, Head of the Institute of Economic Policy at Johannes Kepler Universitat Linz, captures the limitations of propensity-based methods intuitively (31) (Figure 1).

Thus, the authors’ conclusions (while appropriate to the rigorous methodology) are unlikely to be replicable in a randomized trial. Problematically, sufficient equipoise about short-term outcomes no longer exists, making it difficult to justify a new 5-year randomized trial of dexmedetomidine vs placebo in cardiac surgery patients. As the evidence evolves, the role of observational data may have to increase, in the search for “the right population” for this therapy. Residual confounding, particularly with very-long-term outcomes, will be a perpetual problem in the absence of randomized trials.

## Conclusion

So, what is the silver bullet strategy for these patients? We don’t yet know. As with any other clinical question, the risks and benefits of an intervention must be weighed, and dexmedetomidine, even at low doses, clearly confers clinically significant risks of hypotension and bradycardia. In the post-cardiac surgical population, this exposes patients to extended use of pressors, chronotropes and pacing techniques, all of which confer their own risks. Unless true, independent, benefit of dexmedetomidine can be shown, the compensation for these side-effects adds unnecessary complexity in this patient population.

Nonetheless, we have not yet eliminated the possibility, which is based on strong mechanistic hypotheses but weak clinical evidence, that dexmedetomidine may offer meaningful protection against post-operative delirium in some subsets of the cardiac surgical population. The heterogeneity, concern for bias and inconclusive nature of the extant of the data do not yet allow a definitive answer as to *who* would benefit, from *how much* dexmedetomidine, administered *how*, and during *which point* of the perioperative period. While ongoing trials may provide further illumination, dexmedetomidine remains a silver bullet in search of its perfect werewolf.

## Financial support and sponsorship:

ELW was supported by KL2TR001870 from the National Institute for Advancing Translational Sciences of the National Institutes of Health, R01AG079263 from the National Institute on Aging of the National Institutes of Health. Both authors were supported by the UCSF Department of Anesthesia & Perioperative Care.

## References:

1. Crocker E, Beggs T, Hassan A et al. Long-term effects of postoperative delirium in patients undergoing cardiac operation: A systematic review. Ann Thorac Surg 2016 Oct; 102(4):1391–9. [PubMed: 27344279]

*2. Chitnis S, Mullane D, Brohan J,N et al. Dexmedetomidine Use in Intensive Care Unit Sedation and Postoperative Recovery in Elderly Patients Post-Cardiac Surgery (DIRECT). J Cardiothorac Vasc Anesth. 2022 Mar;36(3):880–92. [PubMed: 34887180] This open-label study randomized n=70 patients age 75 and older to receive either propofol or dexmedetomidine starting at sternal closure through ICU admission. The primary outcome, quality of recovery at 3 days, was not different between the groups; however, the delirium outcome - although a priori underpowered - showed a potential clinically significant benefit of dexmedetomidine (delirium: 42% in propofol, vs 24% with dexmedetomidine; p=0.19). Nonetheless, the trial's small size means the dexmedetomidine finding is subject to random variability, and should not be taken as definitive. The authors' use of a patient-centered outcome, quality of recovery, as primary should be applauded, however; they fairly conclusively excluded the potential for clinically significant recovery benefit for dexmedetomdine. If delirium was prevented by dexmedetomidine, other issues with postoperative recovery kept the theoretical benefits of delirium prevention from being clinically apparent.

3. American Psychiatric Association Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed2013; Arlington, VA: American Psychiatric Association,.

4. Ueki M, Kawasaki T, Habe K, et al. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia. 2014;69(7):693–700. [PubMed: 24773263]

5. Ji F, Li Z, Nguyen H, Young N, et al. Perioperative dexmedetomidine improves outcomes of cardiac surgery. Circulation. 2013 Apr 16;127(15):1576–84. [PubMed: 23513068]

6. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg. 2012 Jul;27(4):481–92. [PubMed: 22784203]

7. Arora RC, Djaiani G, Rudolph JL. Detection, Prevention, and Management of Delirium in the Critically Ill Cardiac Patient and Patients Who Undergo Cardiac Procedures. Can J Cardiol. 2017 Jan 1;33(1):80–7. [PubMed: 28024558]

8. Maldonado JR, Wysong A, van der Starre PJA, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2009 Jun;50(3):206–17. [PubMed: 19567759]

9. MacLullich AM, Ferguson KJ, Miller T, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res. 2008 Sep;65(3):229–38. [PubMed: 18707945]

10. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. Clinical Pharmacokinetics 2017; 56:893–913. [PubMed: 28105598]

11. Zhao S, Wu W, Lin X, et al. Protective effects of dexmedetomidine in vital organ injury: crucial roles of autophagy. Cell Mol Biol Lett. 2022 May 4;27(1):34. [PubMed: 35508984]

12. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients: A Randomized Trial. JAMA. 2009 Feb 4;301(5):489–99. [PubMed: 19188334]

13. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med. 2018 May;197(9):1147–56. [PubMed: 29498534]

14. Liu X, Xie G, Zhang K,Set al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care. 2017 Apr;38:190–6. [PubMed: 27936404]

15. Sheikh TA, Dar BA, Akhter N, Ahmad N. A Comparative Study Evaluating Effects of Intravenous Sedation by Dexmedetomidine and Propofol on Patient Hemodynamics and Postoperative Outcomes in Cardiac Surgery. Anesth Essays Res. 2018 Jun;12(2):555–60. [PubMed: 29962634]

16. Shi C, Jin J, Qiao L, et al. Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: a double-blinded, multi-center, randomized study. Clin Interv Aging. 2019;14:571–5. [PubMed: 30936687]

17. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. PloS One. 2017;12(2):e0170757. [PubMed: 28182690]

18. Soh S, Shim JK, Song JW, et al. Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. Br J Anaesth. 2020 Apr 1;124(4):386–94.

19. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet Lond Engl. 2020 Jul 18;396(10245):177–85.

20. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study. J Cardiothorac Vasc Anesth. 2021 Feb;35(2):449–57. [PubMed: 32265083]

21. Subramaniam B, Shankar P, Shaefi S, et al. 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. JAMA. 2019 Feb 19;321(7):686–96. [PubMed: 30778597]

22. Momeni M, Khalifa C, Lemaire G, et al. Propofol plus low-dose dexmedetomidine infusion and postoperative delirium in older patients undergoing cardiac surgery. Br J Anaesth. 2021 Mar;126(3):665–73. [PubMed: 33358336]

**23. Li P, Li LX, Zhao ZZ, et al. Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2021 May 18;21(1):153. [PubMed: 34006239] Given the difficulty interpreting the mass of individual trials, meta-analysis of this topic is exceptionally helpful. However, differences in meta-analysis methodology have implications for their conclusions. By not eliminating studies at high risk of bias, Li and colleagues summarize the literature "as is," without regard to its limitations. The conclusions of this meta-analysis, which imply that younger patients and a shorter period of use for dexmedetomidine are more likely to be of benefit, are counterintuitive and should prompt a "second look," as was done by the following reference.

**24. Patel M, Onwochei DN, Desai N. Influence of perioperative dexmedetomidine on the incidence of postoperative delirium in adult patients undergoing cardiac surgery. Br J Anaesth. 2022 Jul;129(1):67–83. [PubMed: 35279278] This meta-analysis provides a useful complement to the one above. By eliminating studies at high risk of bias, Patel and colleagues found no benefit of dexmedetomidine in preventing delirium in cardiac surgical patients. The counterintuitive findings found by Li and colleagues, thus, are more likely explained by the underlying trials' less rigorous methodology than by a true, biologically plausible mechanism. This meta-analysis, thus, provides the most high-quality summary evidence supporting the conclusion that dexmedetomidine should not, at present, be used to prevent delirium in a broad population of cardiac surgical patients.

25. Duan X, Coburn M, Rossaint R, et al. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth. 2018 Aug;121(2):384–97. [PubMed: 30032877]

26. Wang J, Mao G, Malackany N, et al. Association between perioperative hypotension and postoperative delirium and atrial fibrillation after cardiac surgery: A post-hoc analysis of the DECADE trial. J Clin Anesth. 2022 Feb;76:110584. [PubMed: 34784557]

27. Neerland BE, Busund R, Haaverstad R, et al. Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after open heart surgery (ALPHA2PREVENT): protocol for a multicentre randomised controlled trial. BMJ Open. 2022 Jun 20;12(6):e057460.

28. Gargadennec T, Oilleau JF, Rozec B, et al. Dexmedetomidine after Cardiac Surgery for Prevention of Delirium (EXACTUM) trial protocol: a multicentre randomised, double-blind, placebo-controlled trial. BMJ Open. 2022 Apr 8;12(4):e058968.

29. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018 Sep;46(9):e825. [PubMed: 30113379]

*30. Peng K, Shen YP, Ying YY, et al. Perioperative dexmedetomidine and 5-year survival in patients undergoing cardiac surgery. Br J Anaesth 2021 Aug; 127(2):215–223. [PubMed: 34082896] This well-conducted observational study is an excellent example of its type. However, as described in the text, there are major challenges to inferring dexmedetomidine reduces long-term mortality – as this study finds – using observational data alone. The potential for residual confounding is overt when an anesthesiologist's treatment decisions are based on clinical factors which are unmeasured, like severity of disease, frailty, or preexisting delirium, and when other elements of intraoperative treatment may be affected by anesthesiologist quality.

31. Halla M (@HallaMartin). "Yet another one of those illustrations why (propensity score) matching might not do the job #EconTwitter" 12 September 2022, 6:07 AM. Tweet. Available at https://twitter.com/HallaMartin/status/1569311697717927937; accessed 14 September 2022.

**Key points:**

- Dexmedetomidine may prevent postoperative delirium (POD) after cardiac surgery, but the current body of literature to support its widespread use lacks strength and consistency.
- Many of the RCTs in favor of dexmedetomidine for POD prevention in cardiac surgical patients studied POD as a secondary outcome and suffered from bias and heterogeneity; more recent, well-conducted trials have typically shown no benefit.
- If dexmedetomidine is effective for preventing POD, further robust studies to identify the correct dose, timing and target patient population will be needed.
- Current best evidence does not support use of dexmedetomidine for POD prevention.


**Figure 1.**
Illustrative example of the potential role of unmeasured confounding, which is nearly inevitable in propensity-based analytic methods, on risk estimates (31).

**Table 1:**

**Proposed etiologies of delirium:**

Considering the integration of a “3-strike” delirium paradigm in the context of direct brain insults and concomitant aberrant stress responses. With the complexity of the many potential different pathways it is unsurprising that treatment and prevention of delirium has proven to be so elusive. (7-9) Interesting clinical hypotheses, with important implications for the role of dexmedetomidine in cardiac surgical delirium, include the possibility that there exist several different phenotypes of delirium, categorized by inciting event, under the umbrella syndrome of delirium.

| | **Baseline risk** | **Intraoperative stressor** | **Post-surgical Stressor** |
|---|---|---|---|
| Direct brain insults | Dementia<br>Advanced age<br>Vascular disease | Anesthesia<br>anticholinergics<br>Dopaminergic agents<br>GABA agonists<br>opioids<br>hypotension<br>Electrolyte disturbances<br>CPB/procedure<br>Microembolism<br>Ischemia/reperfusion | Hypotension<br>Electrolyte disturbances<br>Sedation<br>GABA agonists<br>opioids<br>Adjunct agents<br>anticholinergics |
| Aberrant stress response | Atherosclerosis<br>Age<br>Frailty/functional status<br>Baseline cognitive function | LHPAA<br>Sympathetic NS (acetylcholine, adrenaline, noradrenaline)<br>Inflammatory system (TNF-a, IL-1b, IL-6, IL-8, PGE2, IFNa/IFNb)<br>BBB disruption | LHPAA<br>Sympathetic NS (acetylcholine, adrenaline, noradrenaline)<br>Inflammatory system (TNF-a, IL-1b, IL-6, IL-8, PGE2, IFNa/IFNb)<br>BBB disruption |

LHPAA (Limbic-hypothalamic-pituitary-adrenal axis, NS: nervous system TNF-α: tumor necrosis factor alpha; IL: interleukin; IFN: interferon, PGE2 prostaglandin E2, BBB: blood brain barrier

**Table 2:**

Summary table of exemplar relevant, recent RCTs. Collection of studies are notable for high degree of heterogeneity with respect to dexmedetomidine timing and dosing, patient age, primary outcomes, POD assessment methods and composition of controls.

| Author | Year | Age | Sample size | Delirium assessment | Dex protocol | Control | Primary outcome | Results |
|---|---|---|---|---|---|---|---|---|
| Intraoperative Dex | | | | | | | | |
| Sheikh(15) | 2018 | 15-60 | 60 | Defined by authors | Bolus: 1mcg/kg<br>Infusion: 02.-0.6 mcg/kg/hr | propofol | "Hemodynamic variables and postoperative outcomes" | Decreased POD with Dex |
| Shi*(16) | 2019 | >=60 | 164 | CAM | Infusion 0.4 – 0.6 mcg/kg/hr + propofol + remifentanil | Propofol + remifentanil | POD | No difference |
| Intraoperative + Postoperative | | | | | | | | |
| Li(17) | 2017 | >=60 | 285 | CAM/CAM-ICU | Intraoperative infusion: 0.4-0.6 mcg/kg/hr<br>Postoperative: 0.1 mcg/kg/hr | NS | POD | No difference |
| Soh(18) | 2020 | >=20 | 108 | DSM or CAM-ICU | Infusion: 0.4 mcg/kg/hr from Anesthetic induction – 24hr post-induction | NS | AKI | No difference |
| Turan(19)(DECADE) | 2020 | 18-85 | 794 | RASS + CAM-ICU | Infusion:<br>0.1 mcg/kg/hr (prior to incision)<br>0.2 mcg/kg/hr after CPB<br>0.4 mcg/kg/hr x 24hrs postop | NS | **Co-primary:<br>New-onset Afib<br>POD | No difference |
| Likhvantsev(20) | 2021 | >45 | 169 | CAM-ICU | Infusion:<br>Intraoperative – 0.7mcg/kg/hr<br>Postoperative – 0.4 mcg/kg/hr | NS | POD | Decreased POD with Dex |
| Postoperative | | | | | | | | |
| Subramaniam(21) DEXACET) | 2019 | >=60 | 120 | CAM/CAM-ICU | Bolus 0.5 – 1mcg/kg; infusion: 0.1-1.4mcg/kg/hr | propofol | POD | No difference |
| Momeni(22) (LOWDEXEL) | 2021 | >=60 | 420 | CAM-ICU, chart review | Infusion: 0.4mcg/kg/hr (chest closure – 10 hr) + Propofol | Propofol + NS | POD | No difference |
| Chitnis(2)(DIRECT) | 2022 | >75 | 70 | ICDSC | Infusion: 0.5mcg/kg/hr (range 0 – 1.5mcg/kg/hr) | Propofol | Quality of Recovery | No difference*** |

*Study retracted due to registration violation

**Powered for new-onset Afib, stopped early for futility

***Underpowered for POD

NS: normal saline, Dex: dexmedetomidine, Prop: propofol, CAM: Confusion Assessment Method, POD: Postoperative Delirium, DSM: Diagnostic and Statistical Manual of Mental Disorders, CPB: Cardiopulmonary bypass, RASS: Richmond Agitation and Sedation Scale, ICDSC: Intensive Care Delirium Screening Checklist

**Table 3:**

Summary table of recent meta-analyses. Methodology in meta-analysis, like methodology in trial design, has important implications for the overall conclusion.

| Author | Literature search dates | Adjusted for bias? | Contribution |
|---|---|---|---|
| Liu(14) | Up to May 23, 2016 | No – all included studies carried “high risk” due to lack of blinding | Showed statistically significant lower incidence of POD with dexmedetomidine compared to propofol sedation. Made the argument for more robust RCTs. Raised the question of associated risks, including bradycardia. |
| Li(23) | Up to August 27, 2020 | No – Included studies ranged from low to high * | Showed statistically significant lower incidence of POD with dexmedetomidine vs. control. Highlighted the need to identify the correct timing of administration and target patient population. |
| Patel(24) | Up to April 18, 2021 | Yes | Showed statistically significant lower incidence of POD with dexmedetomidine vs. control when considering all included studies. Effect vanished when studies with high risk of bias were excluded. Highlighted need for robust, methodically sound RCTs for definitive answer. |

* Several studies had domains within the Cochrane Risk of Bias Method with insufficient data to make a determination