

6. Garrity AG, Botta S, Lazar SB, Swor E, Vanini G, Baghdoyan HA, Lydic R: Dexmedetomidine-induced sedation does not mimic the neurobehavioral phenotypes of sleep in Sprague Dawley rat. *Sleep* 2015; 38:73–84
7. Carrasco G, Baeza N, Cabré L, Portillo E, Gimeno G, Manzanedo D, Calizaya M: Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in nonintubated ICU patients: A nonrandomized controlled trial. *Crit Care Med* 2016; 44:1295–306

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## Low-dose, Nontitrated Dexmedetomidine Trials: Clarifying Possible Coenrollment

To the Editor:

In the November 2016 issue of *ANESTHESIOLOGY*, Wu *et al.*<sup>1</sup> reported the results of their randomized controlled trial of low-dose (0.1 µg kg<sup>-1</sup> h<sup>-1</sup>, nontitrated) dexmedetomidine in 76 nonmechanically ventilated noncardiac surgery patients aged 65 yr or older (an off-label use), in which dexmedetomidine was found to improve several polysomnographic and self-reported indices of sleep quality. In August 2016, the same group published in the *Lancet* the results of an identical drug protocol applied to 700 patients meeting almost identical inclusion/exclusion criteria.<sup>2</sup> This *Lancet* paper reported a significantly lower incidence of delirium in patients treated with dexmedetomidine compared to the control group, along with several congruent secondary endpoints such as improved subjective sleep quality. One of the two *Lancet* trial sites, the Peking University First Hospital, was also the location of the *ANESTHESIOLOGY* study. Patients in the *ANESTHESIOLOGY* study were recruited exclusively during the time that the *Lancet* study was underway in the same hospital. In their Consolidated Standards of Reporting Trials (CONSORT) patient flow diagrams, neither paper indicates that any patients were excluded because they were enrolled in another trial. It could therefore appear, as published, that the results from some patients have been reported twice, rather than that the two papers report entirely separate experimental series. Duplicate publication without acknowledgment overstates the evidence and could, for example, lead a meta-analysis to the wrong conclusion. Both publications report important (indeed, potentially practice-changing) data from well-conducted trials. It would be helpful for the authors to address this potentially superficially misleading appearance and clarify that patients could not, in fact, be enrolled in both trials, perhaps also indicating how patients were chosen for enrollment in one study in preference to the other.

### Competing Interests

Prof. Reade reports receiving a single fee in 2009 to contribute to a Hospira (Melbourne, Australia) clinician advisory board preparing guidelines for the use of dexmedetomidine

and a single fee plus travel expenses in 2016 to present the results of the Dexmedetomidine to Lessen ICU Agitation (DahLIA) trial (clinical trial no. NCT01151865) to an educational meeting funded by Pfizer (Melbourne, Australia). Pfizer has provided unrestricted sponsorship for both the DahLIA and Sedation Practice in Intensive Care Evaluation (SPICE) (clinical trial no. NCT01728558) trials, in which Prof. Reade is a chief investigator.

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### References

1. Wu XH, Cui F, Zhang C, Meng ZT, Wang DX, Ma J, Wang GF, Zhu SN, Ma D: Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: A pilot randomized controlled trial. *ANESTHESIOLOGY* 2016; 125:979–91
2. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D: Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: A randomized, double-blind, placebo-controlled trial. *Lancet* 2016; 388:1893–902

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In Reply:

We agree with Dr. Goucher *et al.* that low-dose dexmedetomidine infusion did not restore the normal sleep architecture because stage 3 non-rapid eye movement sleep and rapid eye movement (REM) sleep remained significantly decreased or absent in our patients.<sup>1</sup> This is also the case when dexmedetomidine was administered for sedation in mechanically ventilated patients.<sup>2,3</sup> It should be noted that the target subjects were patients in the intensive care unit (ICU) after major surgery in our study<sup>1</sup> or receiving mechanical ventilation in another previous study.<sup>3</sup> It is well known that significant sleep disturbances such as fragmented sleep, decreased sleep efficiency, increased stage 1 non-REM sleep, and decreased or absent stage 3 non-REM and REM sleep are often present in those patients. Dexmedetomidine partially improved “sleep architecture” through increasing the percentage of stage 2 non-REM sleep (and decreasing the percentage of stage 1 non-REM sleep), a unique property that has also been demonstrated in other clinical studies previously.<sup>4</sup>

Considering the importance of sleep for ICU recovery and the lack of effective pharmacologic interventions to improve sleep,<sup>5</sup> prophylactic low-dose dexmedetomidine may be a choice, although not the best. Clinical effectiveness was demonstrated in our previous trial in 700 patients admitted to the ICU after noncardiac surgery, in which low-dose dexmedetomidine infusion reduced the incidence of delirium during the first 7 days after surgery (9% compared with 23% with placebo) and also decreased the incidence of nondelirium complications and increased early hospital discharge.<sup>6</sup> We cannot establish a causal relationship between

delirium reduction and improved sleep in patients from these two independent trials.<sup>1,6</sup>

It is true that hemodynamic disturbances are major concerns when using dexmedetomidine in ICU patients. Indeed, dexmedetomidine at such a low dose (0.1  $\mu\text{g kg}^{-1} \text{h}^{-1}$ ) slightly increased the occurrence of hypotension, although not statistically significantly,<sup>6</sup> indicating that close monitoring is necessary whenever dexmedetomidine is on-board. Last but not least, whether delirium prevention by dexmedetomidine ultimately improves patients' long-term outcome remains unknown and warrants further study.

Regarding the question of Dr. Reade, herein we confirm that these two studies<sup>1,6</sup> are completely independent trials in which each has an individual registration (Chinese Clinical Trial Registry [Chengdu, Sichuan, China; www.chictr.org.cn] Nos. ChiCTR-TRC-10000802 and ChiCTR-TRC-12002567). Patients who were recruited in one study were not enrolled the other one.

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### Competing Interests

Dr. Wang reports that he has received lecture fees and travel expenses for lectures given at domestic academic meetings from Jiangsu Hengrui Medicine Co., Ltd. (Jiangsu, China). The other author reports no competing interests.

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### References

1. Wu XH, Cui F, Zhang C, Meng ZT, Wang DX, Ma J, Wang GF, Zhu SN, Ma D: Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: A pilot randomized controlled trial. *ANESTHESIOLOGY* 2016; 125:979–91
2. Oto J, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M: Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; 38:1982–9
3. Alexopoulou C, Kondili E, Diamantaki E, Psarologakis C, Kokkini S, Bolaki M, Georgopoulos D: Effects of dexmedetomidine on sleep quality in critically ill patients: A pilot study. *ANESTHESIOLOGY* 2014; 121:801–7
4. Huupponen E, Maksimov A, Lapinlampi P, Särkelä M, Saastamoinen A, Snapir A, Scheinin H, Scheinin M, Meriläinen P, Himanen SL, Jääskeläinen S: Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand* 2008; 52:289–94
5. Kanji S, Mera A, Hutton B, Burry L, Rosenberg E, MacDonald E, Luks V: Pharmacological interventions to improve sleep in hospitalised adults: A systematic review. *BMJ Open* 2016; 6:e012108

6. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D: Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: A randomised, double-blind, placebo-controlled trial. *Lancet* 2016; 388:1893–902

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## Is the PeriOperative ISchemic Evaluation-2 Trial Equipoised?

To the Editor:

We read with interest the article by Eikelboom *et al.*<sup>1</sup> reporting the results of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial regarding postoperative incidence of venous thromboembolism (VTE).

We had several concerns:

- (1) It seemed to us unusual to report the findings of a randomized clinical trial and to pool its results immediately with previous trials and meta-analyses in the same article. Is there a rationale for not reporting the findings of POISE-2 alone, knowing that the pooling part was not specified in the protocol of the study posted on clinicaltrials.gov (NCT01082874)?
- (2) Referring to the design of POISE-2 published in 2014,<sup>2</sup> the trial outcomes were listed in appendix A of that article. Pulmonary embolism and deep venous thrombosis at 30 days were defined as tertiary outcomes and pulmonary embolism and deep venous thrombosis at 1 yr as secondary outcomes. In this understanding, POISE-2 was not specifically designed to assess the effect of aspirin on VTE.
- (3) Determination of the POISE-2 sample size was based on the assumption of a hazard ratio of 0.75 for the primary composite outcome (mortality and nonfatal myocardial infarction), two-sided  $\alpha$  of 0.05, power of 0.80, and base incidence of composite outcome approximately 6%. However, as stated by the authors in the introduction, incidence of symptomatic postoperative VTE in noncardiac surgical patients is 1 to 5% in the absence of prophylactic anticoagulation, and one would be inclined to consider the lower bound with the current use of prophylactic anticoagulation (an assumption confirmed by the results of POISE-2,<sup>1</sup> reporting an incidence of 1.2%). Keeping the other parameters constant ( $\alpha$ , power, and effect size), at least 36,000 subjects would be needed to enable rejecting the null hypothesis. As a corollary, the *post hoc* power determination yields a 30% power for POISE-2 to detect an effect of aspirin on VTE, far less than the 50% estimation given by the authors in the discussion.