Randomized Controlled Trial

Effects of perioperative rosuvastatin on postoperative delirium in elderly patients: A randomized, double-blind, and placebo-controlled trial

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Institutional review board statement: The study protocol was approved by the Clinical Research Ethics Committees of Anhui Medical University Affiliated with Wuxi Clinical College (ChiCTR-IPR-17011984 and YXLL-2017-02). The study protocol received Ethics Committee approval from all participating centers. Written informed consent was obtained from patients whose competence was established by their accurate orientation for time, place, and person, as well as an understanding of the recruiter’s description of the trial, or otherwise from their next of kin or their legal representative.

Abstract

BACKGROUND
Experimental evidence has indicated the benefits of statins for the treatment of postoperative delirium. Previously, clinical trials did not reach definite conclusions on the effects of statins on delirium. Some clinical trials have indicated that statins reduce postoperative delirium and improve outcomes, while some studies have reported negative results.

AIM
To evaluate whether perioperative rosuvastatin treatment reduces the incidence of delirium and improves clinical outcomes.

METHODS
This randomized, double-blind, and placebo-controlled trial was conducted in a single center in Jiangsu, China. This study enrolled patients aged greater than 60 years who received general anesthesia during elective operations and provided informed consent. A computer-generated randomization sequence (in a 1:1 ratio) was used to randomly assign patients to receive either rosuvastatin (40 mg/d) or placebo. Participants, care providers, and investigators were all masked to group assignments. The primary endpoint was the incidence of delirium, which was assessed twice daily with the Confusion Assessment Method during the first 7 postoperative days. Analyses were performed on intention-to-treat and safety populations.

RESULTS
Between January 1, 2017 and January 1, 2020, 3512 patients were assessed. A total
of 821 patients were randomly assigned to receive either placebo \( (n = 411) \) or rosuvastatin \( (n = 410) \). The incidence of postoperative delirium was significantly lower in the rosuvastatin group \([23 (5.6\%) \) of 410 patients \] than in the placebo group \([42 (13.5\%) \) of 411 patients \] [odds ratios (OR) = 0.522, 95% confidence interval (CI): 0.308-0.885; \( P < 0.05 \)]. No significant difference in 30-d all-cause mortality \((6.1\% \text{ vs } 8.7\%, \text{ OR} = 0.67, \text{ 95\%CI: 0.39-1.2, } P = 0.147) \) was observed between the two groups. Rosuvastatin decreased the hospitalization time \((13.8 \pm 2.5 \text{ vs } 14.2 \pm 2.8, \text{ P = 0.03} \) and hospitalization expenses \((9.3 \pm 2.5 \text{ vs } 9.8 \pm 2.9, \text{ P = 0.007} \). No significant differences in abnormal liver enzymes \((9.0\% \text{ vs } 7.1\%, \text{ OR} = 1.307, \text{ 95\%CI: 0.787-2.169, } P = 0.30) \) or rhabdomyolysis \((0.73\% \text{ vs } 0.24\%, \text{ OR} = 3.020, \text{ 95\%CI: 0.31-29.2, } P = 0.37) \) were observed between the two groups.

**CONCLUSION**

The current study suggests that perioperative rosuvastatin treatment reduces the incidence of delirium after an elective operation under general anesthesia. However, the evidence does not reveal that rosuvastatin improves clinical outcomes. The therapy is safe. Further investigation is necessary to fully understand the potential usefulness of rosuvastatin in elderly patients.

**Key Words:** Perioperative rosuvastatin; Postoperative delirium; Elderly; General anesthesia; Randomised controlled trial

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**INTRODUCTION**

Delirium is a severe clinical syndrome characterized by a temporary organic mental disorder, acute brain dysfunction, changes in cognition, and disturbances in orientation, which may induce long-term cognitive impairment and death/disability. This randomized, double-blind, and placebo-controlled trial indicated that perioperative rosuvastatin treatment can significantly decrease the incidence of delirium after an elective operation under general anesthesia, and reduce the hospitalization time and hospitalization expenses, but did not improve the clinical outcomes.
promote neuroprotection.[7-11] As the neuroprotection-related molecular mechanism is similar to the molecular mechanism of delirium, statins may prevent delirium. A retrospective, single-center study that included 1132 vascular surgical patients confirmed that preoperative statins significantly decrease the incidence of postoperative delirium.[12] Another observational cohort study including 4659 consecutive patients after coronary revascularization at two university institutions concluded that preoperative statins do not decrease the incidence of delirium,[13] and a meta-analysis indicated no protective effects of statins against perioperative stroke.[14] However, two very important and authoritative randomized controlled trials (NCT00979121 and NCT00719446) enrolled 568 patients (293/275) at 35 hospitals in the United States and showed no benefit of rosuvastatin in reducing delirium or cognitive impairment in the intensive care unit (ICU) during 12 mo of follow-up.[15] Evidence from randomized controlled studies of the effects of statins on delirium in elderly surgical patients after general anesthesia is lacking. Moreover, researchers have not clearly determined whether rosuvastatin exerts preventive effects on delirium. The present study, therefore, explored whether acute rosuvastatin treatment reduces postoperative delirium and improves clinical outcomes in surgical patients after general anesthesia.

MATERIALS AND METHODS

Study design

This randomized, double-blind, and parallel-arm placebo-controlled trial was conducted at a single center in Jiangsu, China between January 1, 2017 and January 1, 2020, and 3512 patients were assessed. Anhui Medical University Affiliated with Wuxi Clinical College (904th Hospital of PLA) was the study center. The study was registered in chictr.org.cn with number ChiCTR-IPR-17011984 (registration date: July 13, 2017). The study was designed to assess the superiority of the intervention. The study protocol was approved by the Clinical Research Ethics Committees of Anhui Medical University Affiliated with Wuxi Clinical College (YXLL-2017-02). The study protocol received Ethics Committee approval from all participating centers. Written informed consent was obtained from patients whose competence was established by their accurate orientation for time, place, and person, as well as an understanding of the recruiter’s description of the trial or otherwise from their next of kin or legal representative.

All patients were randomly assigned (1:1) to receive 40 mg/d rosuvastatin or placebo within 7 d after surgery and 3 d before surgery (Figure 1). Rosuvastatin or placebo was administered orally. Delirium was assessed twice daily with the Confusion Assessment Method (CAM) during the first 7 postoperative days. The final follow-up was 30 d after surgery.

Study patients

Eligible patients were greater than 60 years old who underwent joint replacement surgery in the ICU. The inclusion criteria were: (1) Aged more than 60 years; (2) Able to be randomized and receive rosuvastatin or placebo within 10 d during the perioperative period; and (3) Received general anesthesia and were admitted to the ICU. The exclusion criteria were: (1) Likely unsalvageable patients identified at admission; (2) High cholesterol levels combined with diabetes; (3) Brain injury or neurosurgery; (4) Severe sinus bradycardia; (5) Neurological disease; (6) Abnormal liver enzymes, and patients with rhabdomyolysis and myopathy; (7) Patients with a history of mental illness and epilepsy; (8) Patients with severe lung disease and multiple organ dysfunction; and (9) Other reasons identified by the researchers.

Randomization and masking

The patients were randomized into the rosuvastatin group (40 mg/d, 10 d) or the placebo group using fixed randomization schemes with random numbers (in a 1:1 ratio) according to a computer system created. An independent statistician who was blinded in the trial finished this process. All drugs were identical in appearance and packaged in identical medical envelopes, and the medication was given by the nurse according to the randomization sequence. To ensure patient safety, the group allocation could be unblinded with two on-call experts or pharmacist if severe adverse events or any unexpected deterioration in the patient’s clinical status occurred, and all situations need to be documented in the case report forms. Patients and all investigators giving treatments and assessing outcomes were blinded to treatment allocation.
Procedures

No premedication was administered. All patients underwent a standard preoperative evaluation and were assigned an American Society of Anesthesiologists classification based on their medical comorbidities. All patients received the same general anesthesia protocol. Intravenous (IV) midazolam (1-2 mg) and fentanyl (50-100 mcg) were administered for preoperative sedation, and anesthesia was maintained with 3 to 6 mcg/kg IV fentanyl. All patients were routinely monitored with electrocardiography, noninvasive blood pressure, pulse oximetry (SpO₂), and bispectral index. Radial arterial pressure and central venous pressures were monitored as necessary.

After surgery, the patients were admitted to the ICU, and all patients received the same management. Patients in the treatment group received 40 mg/d rosuvastatin, while the placebo group received an equal amount of starch. All study drugs (rosuvastatin and placebo) were provided by Zhejiang Jingxin Medicine Co, Ltd. (Zhejiang, China).

Outcome assessment

All investigators assessing the outcomes and collecting the data were blinded to treatment allocation. All investigators need to be trained before the study and not participate in the treatment of patients. The incidence of delirium at the first 7 d after surgery was the primary endpoint. The first postoperative evaluation of delirium was performed approximately 24 h after surgery twice daily[16,17]. Delirium was assessed using the CAM and the CAM for the ICU (CAM-ICU). Both the CAM and CAM-ICU detect four features of delirium: (1) Acute onset of mental status changes or a fluctuating course; (2) Inattention; (3) Disorganized thinking; and (4) An altered level of consciousness. A patient must display features 1 and 2, with either feature 3 or 4 to be diagnosed with delirium[18]. If patients died or discharged within 7 d after surgery, then the last delirium assessment was missing[16]. The secondary endpoints included all-cause 30-d mortality, length of stay in the ICU, the occurrence of nondelirium postoperative complications, and hospital costs.

Assessment of rosuvastatin-related adverse events

The most common adverse events include abnormal liver enzyme levels, rhabdomyolysis, and myopathy. We evaluated all related adverse events and groups were unblinded if necessary.

Statistical analysis

The sample size was according to the previous study published in 2014; we set a type I error of 0.05, and 80% power, then 739 patients were required to detect a difference [19]. Further assuming a 10% loss to follow-up, 845 patients were enrolled. Clinical data of all patients were collected by specialized nurses and stored in a database. This study described the incidence and relative risk reduction of dichotomous variables for the rosuvastatin-treated group relative to the placebo group, with the corresponding 95% confidence interval (CI). Normally distributed continuous data are presented as the mean ± SD and were analyzed using the unpaired t-test. Non-normally distributed data were compared by an independent-samples Mann-Whitney U test. Categorical
data were compared using the χ² test, or continuity correction χ² test. We calculated mean differences or risk ratios with two-sided 95% CIs. P < 0.05 indicated statistical significance. Statistical analyses were performed using IBM SPSS Statistics (version 18, SPSS, Chicago, IL, United States). This study did not perform an interim analysis. The Clinical Research Ethics Committee from the 904th Hospital of Joint Logistic Support Force of PLA was involved in overseeing the data.

RESULTS
Between January 1, 2017 and January 1, 2020, 3512 patients were assessed. Eight hundred and twenty-one patients were randomly assigned to receive either placebo (n = 411) or rosuvastatin (n = 410) (Figure 2). The two groups were similar in baseline characteristics without significant differences (Table 1). During the study period, no patients withdrew consent. Thirty-five patients (16 patients in the placebo group and 19 patients in the rosuvastatin group) were lost to follow-up or had clinical data collected at 30 d. In the final intention-to-treat analysis, 786 patients were included (Figure 2). The last randomized patient attended the final follow-up visit on October 31, 2020.

Baseline patient characteristics: Overall population
A total of 3512 patients were enrolled in the present trial, of whom 821 were eligible for this study: 410 (50%) were assigned to the rosuvastatin group, and 411 (50%) were assigned to the placebo group. Patient demographics and baseline characteristics were not significantly different between the two groups. The general anesthetic medication, anesthesia time, and operative time were also similar between the two groups. Postoperative medication and management were also similar (Table 1).

Primary endpoint-clinical outcomes
The incidence of postoperative delirium was 23 (5.6%) of 410 patients in the rosuvastatin group, and 42 (13.5%) of 411 patients experienced delirium in the placebo group [odds ratios (OR) = 0.522, 95%CI: 0.308-0.885, P < 0.05; Figure 3].

Secondary endpoints
Many previous studies have reported that delirium increases 30-d all-cause mortality, hospitalization time, and hospitalization expenses. Thus, the present study also evaluated the differences between the two groups in 30-d all-cause mortality, hospitalization time, and hospitalization expenses. Regarding 30-d all-cause mortality, 24 (6.1%) of 391 patients in the rosuvastatin group and 35 (8.7%) of 395 in the placebo group died (OR = 0.67, 95%CI: 0.39-1.2, P = 0.147; Figure 4). Hospitalization time was significantly increased in the placebo group compared to that in the rosuvastatin group (13.8 ± 2.5 vs 14.2 ± 2.8, P = 0.03; Figure 5). Similarly, hospitalization expenses of the placebo group were significantly higher than those of the rosuvastatin group (9.3 ± 2.5 vs 9.8 ± 2.9, P = 0.007; Figure 6).

Safety evaluation
We evaluated drug-related complications, including abnormal liver enzyme levels and rhabdomyolysis. The occurrence of postoperative abnormal liver enzyme levels was not significantly different between the two groups (9.0% vs 7.1%, OR = 1.307, 95%CI: 0.787-2.169, P = 0.30; Table 2). The occurrence of rhabdomyolysis in the placebo group and rosuvastatin group showed no differences (0.73% vs 0.24%, OR = 3.020, 95%CI: 0.31-29.2, P = 0.37; Table 2). Although no statistically significant differences in abnormal liver enzyme levels or rhabdomyolysis were observed between the two groups, the incidence of postoperative complications in the rosuvastatin group was higher than that in the placebo group, which requires attention to avoid serious complications.

DISCUSSION
As shown in the present study, rosuvastatin significantly decreased postoperative delirium in elderly surgical patients under general anesthesia. Meanwhile, rosuvastatin also reduced the length of the hospital stay and hospitalization expenses. Based on our data, rosuvastatin did not affect 30-d all-cause mortality. The incidences...
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Table 1 Demographic and baseline characteristics of the study population

| Group                              | Place group | Rosuvastatin group | P value |
|------------------------------------|-------------|--------------------|---------|
| Number of patients                 | 411         | 410                |         |
| Age (mean ± SD)                    | 66.5 ± 5.3  | 66.3 ± 5.1         | 0.664   |
| Gender, n (%)                      |             |                    | 0.243   |
| Male                               | 186 (45.3)  | 169 (41.2)         |         |
| Female                             | 225 (54.7)  | 241 (58.8)         |         |
| History of hypertension, n (%)     |             |                    | 0.623   |
| Yes                                | 109 (26.5)  | 115 (28.0)         |         |
| No                                 | 302 (73.5)  | 295 (72)           |         |
| History of diabetes, n (%)         |             |                    | 0.558   |
| Yes                                | 88 (21.4)   | 81 (19.8)          |         |
| No                                 | 323 (78.6)  | 329 (80.2)         |         |
| Nicotine use, n (%)                |             |                    | 0.518   |
| Yes                                | 72 (17.5)   | 79 (19.3)          |         |
| No                                 | 339 (82.5)  | 331 (80.7)         |         |
| Type of surgery, n (%)             |             |                    | > 0.05  |
| Thoracic operation                 | 77 (18.7)   | 69 (16.8)          |         |
| Abdominal operation                | 93 (22.6)   | 105 (25.6)         |         |
| Orthopedic operation               | 158 (38.4)  | 142 (34.6)         |         |
| Gynecological operation            | 44 (10.7)   | 58 (14.4)          |         |
| Others                             | 39 (9.6)    | 36 (8.6)           |         |
| Duration of anesthesia (min)       | 114.0 ± 42.7| 115.5 ± 42.2       | 0.625   |
| Blood transfusion during surgery, n (%) |         |                    | 0.660   |
| Yes                                | 48 (11.7)   | 52 (12.7)          |         |
| No                                 | 363 (88.3)  | 358 (87.3)         |         |
| Intraoperative medication, n (%)   |             |                    | > 0.05  |
| Midazolam                          |             |                    |         |
| Fentanyl                           | 411 (100)   | 410 (100)          |         |
| Propofol                           | 411 (100)   | 410 (100)          |         |
| Atropine                           | 75 (18.2)   | 79 (19.3)          |         |
| Postoperative analgesics (7 d), n (%) |         |                    | > 0.05  |
| Diclofenac sodium                  | 104 (25.3)  | 99 (24.1)          |         |
| Morphine                           | 85 (20.7)   | 91 (22.2)          |         |
| Midazolam                          | 41 (10.0)   | 57 (13.9)          |         |
| No                                 | 181 (44.0)  | 163 (39.8)         |         |

of postoperative complications, especially drug-related complications, including abnormal liver enzyme levels and rhabdomyolysis, were similar.

Our study reported that the incidence of postoperative delirium was 13.5% in placebo-treated patients and 5.6% in the rosuvastatin group, and the results were similar to those of a large number of previous studies.[12,17,20,21] Liu et al.[22] performed a retrospective cohort study that included 361 elderly patients and reported that 19.9% of noncardiac surgery individuals developed postoperative delirium after surgery. Kant et al.[23] also conducted a study on 413 patients and reported that the incidence of postoperative delirium was as high as 17%, and preoperative brain magnetic resonance imaging features may indicate a predisposition for developing...
### Table 2 Comparison of postoperative complications between the two groups, n (%)

| Variable                  | Place group | Rosuvastatin group | P value |
|---------------------------|-------------|--------------------|---------|
| Number of patients        | 411         | 410                |         |
| Abnormal liver enzymes    | 29 (7.1)    | 37 (9.0)           | 0.30    |
| Rhabdomyolysis            | 1 (0.24)    | 3 (0.73)           | 0.37    |

Figure 2 Trial profile.

Figure 3 The incidence of postoperative delirium. The odds ratios are rounded. Event rate (%) for postoperative delirium. OR: Odds ratios; CI: Confidence interval.

Delirium after major surgery. Humeidan et al.[24] reported that the incidence of delirium was 23.0% in control participants, and the delirium rate in the intervention group was 14.4%. Thus, the incidence of postoperative delirium after general anesthesia is extremely high, and it has seriously affected the operative effect and long-term outcome. In addition, postoperative delirium is associated with high morbidity and mortality rates, worse operative effects, and worse long-term outcomes[2,25]. A previous meta-analysis reported that postoperative delirium increases the risk of a person experiencing poorer outcomes[26]. Additionally, postoperative delirium also leads to a longer hospitalization time and higher hospitalization expenses. Therefore, medication has now become the main treatment.
Many factors may lead to postoperative delirium, and delirium is usually a multifactorial disease\cite{2,27}. Chen et al\cite{27} reported that major surgery, drugs (sedatives or hypnotics), trauma (especially traumatic brain injury), coma, and sleep deprivation are the most important precipitating factors for delirium by performing a literature review and summarized the potential mechanisms of delirium, including systemic neuroinflammation, neurotransmitters, cerebral hypoperfusion, microth-
rombosis, oxidative stress-induced damage, neuronal apoptosis and neuroprotection, endothelial damage, cerebrovascular spasm, and blood-brain barrier injury. Preventing these mechanisms is the key to delirium prevention. Statins, inhibitors of HMG-CoA reductase, have pharmacological mechanisms that include anti-inflammatory and antioxidative stress effects, inhibition of platelet aggregation, and neuroprotection, which are similar to the mechanisms of delirium described above.

According to Yu et al. [26], simvastatin has the potential to be employed as a therapy for depression associated with neuroinflammation by suppressing the activation of microglia and decreasing the expression of proinflammatory cytokines in the hippocampus. Statins reduce the glutamate concentration by upregulating nitric oxide synthase. Jiang et al. [29] also found that statins inhibit 5-HT and 5-HTT expression in patients with chronic obstructive pulmonary disease and pulmonary artery hypertension; then, these drugs may ameliorate delirium by regulating neurotransmitters. Many previous studies have indicated that statins alleviate cerebral vasospasm and cerebral perfusion, prevent endothelial dysfunction, and ameliorate neuronal apoptosis and brain injury [7-11]. Thus, statins may prevent postoperative delirium, and reasonable hypotheses on potential mechanisms have been proposed.

Redelmeier et al. [30] first reported a large sample retrospective cohort study which enrolled 284158 consecutive patients aged > 65 years who were admitted for elective surgery, and found that statins may increase the risk of postoperative delirium among elderly patients. Katznelson et al. [31] reported another study of 1059 patients and indicated that preoperative statins may reduce the odds of postoperative delirium after cardiac surgery with cardiopulmonary bypass. Trezzi et al. [32] reported a retrospective cohort analysis enrolling 12741 patients who underwent cardiac surgery, and the results showed no significant difference between the statin group and the nonstatin group after the cardiac operation. Oh et al. [17] retrospectively reviewed a large cohort of patients who underwent total knee replacement under spinal anesthesia, and continuous perioperative statin use was shown to reduce the risk of delirium after total knee arthroplasty under spinal anesthesia. However, all of these studies were retrospective cohort studies and ultimately did not report uniform and satisfactory results. For postoperative delirium, high evidence-based medicine is not available, and more prospective randomized controlled studies are needed. In recent studies, most large prospective randomized controlled studies have explored the effect of early administration of statins on the prevention and treatment of delirium in critically ill patients or patients undergoing mechanical ventilation [15, 19, 21, 33]. Thus, no related large-sample prospective randomized controlled trials have explored the role of perioperative statins in preventing postoperative delirium in elderly patients who received general anesthesia.

The present study is the first to show that perioperative rosuvastatin treatment potentially reduced the incidence of delirium in patients after an elective operation under general anesthesia and decreased the length of stay in the ICU and hospital costs. Additionally, rosuvastatin did not increase drug-related complications. The study was masked and enrolled 821 patients; most patients completed the follow-up. Another strength of this trial was the double-blind, randomized, and placebo-controlled design (the study was registered at http://www.chictr.org.cn, number: ChiCTR-IPR-17011984). This study has several limitations that need to be improved. Additional clinical factors should be examined, such as sleep quality and pain. The follow-up time in this study was too short and long-term follow-up is required; additionally, the effects on long-term follow-up [34] are also unknown. This study administered a single dose of statins (40 mg/d), and the conventional low dose may not work well.

CONCLUSION

In the present study, the administration of perioperative rosuvastatin may reduce the incidence of delirium in elderly patients after an elective operation under general anesthesia and decrease the length of stay in the ICU and hospital costs. No benefit in terms of the clinical outcome or 30-d all-cause mortality was observed after perioperative rosuvastatin treatment. The effects of longer-term or larger doses of rosuvastatin remain unclear. The effects of longer-term follow-up are also unknown. Further investigation of elderly patients undergoing an elective operation under general anesthesia and treated with different doses of rosuvastatin is needed to fully understand the potential usefulness of rosuvastatin for preventing postoperative delirium.
ARTICLE HIGHLIGHTS

Research background
Our previous basic research study found that statins exert pleiotropic effects, including anti-inflammatory and antioxidative stress effects, inhibition of platelet aggregation, and promotion of neuroprotection. The anti-delirium role of statins was not clearly determined in recent studies.

Research motivation
Delirium is a severe clinical syndrome characterized by a temporary organic mental disorder, which may induce long-term cognitive impairment, death/disability, and increased length of hospital stay and costs. An increasing number of basic research studies indicate that statins play an important role in postoperative delirium. Our preliminary clinical experiment also revealed that perioperative rosuvastatin had potential value as a treatment for postoperative delirium.

Research objectives
This randomized, double-blind, and placebo-controlled trial explored the anti-delirium effect of perioperative rosuvastatin and compared the clinical efficacy and economic efficiency, as well as the safety of perioperative rosuvastatin, in elderly patients who underwent surgery under general anesthesia.

Research methods
This randomized, double-blind, and placebo-controlled trial was conducted in a single center and enrolled patients aged more than 60 years who underwent an elective operation under general anesthesia. The patients were randomly assigned to receive either rosuvastatin (40 mg/d) or placebo.

Research results
The final analysis included 411 patients in the placebo group and 410 patients in the rosuvastatin group. The incidence of postoperative delirium was significantly lower in the rosuvastatin group than in the placebo group ($P < 0.05$). No significant difference in 30-d all-cause mortality was observed between the two groups ($P > 0.05$). Rosuvastatin decreased the hospitalization time and hospitalization expenses ($P < 0.057$). No significant differences in abnormal liver enzyme levels or rhabdomyolysis were observed between the two groups ($P > 0.05$).

Research conclusions
Perioperative rosuvastatin treatment potentially reduces the incidence of delirium after an elective operation under general anesthesia, without a higher incidence of drug-related complications.

Research perspectives
In the future, a large prospective randomized investigation will definitively address the effect of rosuvastatin on postoperative delirium in elderly patients undergoing an elective operation under general anesthesia.

REFERENCES
1 Gleason LJ, Schmitt EM, Kosar CM, Tabloski P, Saczynski JS, Robinson T, Cooper Z, Rogers SO Jr, Jones RN, Marcantonio ER, Inouye SK. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. JAMA Surg 2015; 150: 1134-1140 [PMID: 26352694 DOI: 10.1001/jamasurg.2015.2606]
2 Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014; 383: 911-922 [PMID: 23992774 DOI: 10.1016/S0140-6736(13)60688-1]
3 Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of Dementia After a Concussion. JAMA Neurol 2019; 76: 887-896 [PMID: 31107515 DOI: 10.1001/jamaneurol.2019.1148]
4 Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Fun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW; MIND-USA Investigators. Haloperidol and Ziprasidone for Treatment of Delirium in Critical
Patients After Noncardiac Surgery: A Retrospective Cohort Study. Preoperative Prognostic Nutritional Index Value is Related to Postoperative Delirium in Elderly Liu H
Lancet Respir Med
administration of simvastatin in the prevention and treatment of delirium in critically ill patients Page VJ
Cochrane Database Syst Rev DA, Rose L. Pharmacological interventions for the treatment of delirium in critically ill adults. Burry L
DOI: 10.1002/14651858.CD011749.pub2
Cochrane Database Syst Rev risk of delirium in the critically ill. placebo-controlled trial.
postoperative delirium after joint replacement in elderly patients: a randomized, double-blind, and Zeng ZW
Prevention of Delirium After Total Knee Replacement Under Spinal Anesthesia. Oh TK
DOI: 10.1016/S0140-6736(17)31467-8
Am J Respir Crit Care Med 2016; 388: 1893-1902 [PMID: 27542303 DOI: 10.1016/S0140-6736(16)30580-3]
Oh TK, Park HY, Shin HJ, Jeon YT, Do SH, Hwang JW. The Role of Perioperative Statin Use in the Prevention of Delirium After Total Knee Replacement Under Spinal Anesthesia. J Arthroplasty 2018; 33: 3666-3671. e1 [PMID: 30236494 DOI: 10.1016/j.arth.2018.08.022]
Xuan Y, Fan R, Chen JH, Wang YH, Wu JY, Yang JJ, Luo YC. Effects of dexamethasone for postoperative delirium after joint replacement in elderly patients: a randomized, double-blinded, and placebo-controlled trial. Int J Clin Exp Med 2018; 11: 13147-13157
Page VJ, Davis D, Zhao XB, Norton S, Casarin A, Brown T, Ely EW, McAuley DF. Statin use and risk of delirium in the critically ill. Am J Respir Crit Care Med 2014; 189: 666-673 [PMID: 24417431 DOI: 10.1164/rcrm.201306-1150OC]
Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NK, Cheng W, Ely EW, Egerod I, Fergusson DA, Rose L. Pharmacological interventions for the treatment of delirium in critically ill adults. Cochrane Database Syst Rev 2019; 9: CD011749 [PMID: 31479532 DOI: 10.1002/14651858.CD011749.pub2]
Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, McAuley DF. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2017; 5: 727-737 [PMID: 28734823 DOI: 10.1016/S2213-2600(17)30234-5]
Liu H, Dai M, Guan H, Gao X, Zhou Y, Sun X, Zhou J, Hu X, Li X, Song Y, Han Y, Cao J. Preoperative Prognostic Nutritional Index Value is Related to Postoperative Delirium in Elderly Patients After Noncardiac Surgery: A Retrospective Cohort Study. Risk Manag Healthc Policy 2021;
Xu XQ et al. Perioperative rosuvastatin for postoperative delirium

14: 1-8 [PMID: 33442311 DOI: 10.2147/RMHP.S280567]

Kant IMJ, de Bresser J, van Montfort SJT, Mutsaerts HJM, Witkamp TD, Buijsrogge M, Spies C, Hendrikse J, Slooter AJC. Preoperative brain MRI features and occurrence of postoperative delirium. *J Psychosom Res* 2021; 140: 110301 [PMID: 33260072 DOI: 10.1016/j.jpsychiores.2020.110301]

Humeidan ML, Reyes JC, Mavarez-Martinez A, Roeth C, Nguyen CM, Sheridan E, Zuleta-Alareon A, Otey A, Abdel-Rasoul M, Bergese SD. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium Among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. *JAMA Surg* 2021; 156: 148-156 [PMID: 33175114 DOI: 10.1001/jamasurg.2020.4371]

Kant IMJ, de Bresser J, van Montfort SJT, Mutsaerts HJMM, Witkamp TD, Buijsrogge M, Spies C, Hendrikse J, Slooter AJC. Preoperative brain MRI features and occurrence of postoperative delirium. *J Psychosom Res* 2017; 318: 1161-1174 [PMID: 28973626 DOI: 10.1016/j.jama.2017.12067]

Jiang X, Yuan L, Li P, Wang J, Wang P, Zhang L, Sun B, Sun W. Effect of Simvastatin on 5-HT and 5-HTT in a Rat Model of Pulmonary Artery Hypertension. *Cell Physiol Biochem* 2015; 37: 1712-1724 [PMID: 26544069 DOI: 10.1159/000438536]

Yu XB, Zhang HN, Dai Y, Zhou ZY, Xu RA, Hu LF, Zhang CH, Xu HQ, An YQ, Tang CR, Lin GY. Simvastatin prevents and ameliorates depressive behaviors via neuroinflammatory regulation in mice. *J Affect Disord* 2019; 245: 939-949 [PMID: 30699879 DOI: 10.1016/j.jad.2018.11.086]

Redelmeier DA, Thiruchelvam D, Daneman N. Delirium after elective surgery among elderly patients taking statins. *CMAJ* 2008; 179: 645-652 [PMID: 18809895 DOI: 10.1503/cmaj.080443]

Katznelson R, Djianii GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, Karski J, Mitsakakis N, Carroll J, Beattie WS. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. *Anesthesiology* 2009; 110: 67-73 [PMID: 19104172 DOI: 10.1097/ALN.0b013e3181919b4d]

Trezzi M, Blackstone EH, Sun Z, Li L, Sabik JF 3rd, Lylete BW, Gordon SM, Kohc CG. Statin therapy is associated with fewer infections after cardiac operations. *Ann Thorac Surg* 2013; 95: 892-900 [PMID: 23380476 DOI: 10.1016/j.athoracsur.2012.11.071]

Morandi A, Hughes CG, Thompson JL, Pandharipande PP, Shintani AK, Vasilevskis EE, Han JH, Jackson JC, Laskowitz DT, Bernard GR, Ely EW, Girard TD. Statins and delirium during critical illness: a multicenter, prospective cohort study. *Crit Care Med* 2014; 42: 1899-1909 [PMID: 24810528 DOI: 10.1097/CCM.0000000000000398]

Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, Holman RR. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 2002; 33: 1776-1781 [PMID: 12103531 DOI: 10.1161/01.str.0000020091.07144.c7]

Redelmeier DA, Thiruchelvam D, Daneman N. Delirium after elective surgery among elderly patients taking statins. *CMAJ* 2008; 179: 645-652 [PMID: 18809895 DOI: 10.1503/cmaj.080443]
