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Effect of statins in critically ill adult patients with traumatic brain injury: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091971
Article Type:	Original research
Date Submitted by the Author:	03-Aug-2024
Complete List of Authors:	Veillette, Charles; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada Umana, Mauricio; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada Gagnon, Marc-Aurèle; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Costerousse, Olivier ; Centre de recherche du CHU de Québec-Université Laval, Population Health and Optimal Practices Zarychanski, Ryan ; University of Manitoba, Sections of Critical Care and Hematology/Medical Oncology McAuley, Daniel; Queen's University Belfast, Centre for Experimental Medicine Lawler, Patrick; McGill University Health Centre; University Health Network Lauzier, Francois; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, é English, Shane; Ottawa Hospital Research Institute, Clinical Epidemiology Program; University of Ottawa, Division of Critical Care, Department of Medicine Moore, Lynne; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Isaac, Chartelin-Jean; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Turgeon, Alexis; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada

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Keywords:	Brain Injuries, Drug Therapy, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurological injury < NEUROLOGY, Systematic Review

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Effect of statins in critically ill adult patients with traumatic brain injury: A systematic review and meta-analysis

Charles Veillette MD FRCPC,[1] Mauricio Umana MD,[1] Marc-Aurèle Gagnon MSc,[1] Olivier Costerousse PhD,[1] Ryan Zarychanski MD MSc FRCPC,[2,3] Danny McAuley MD,[4] Patrick Lawler MD MSc FRCPC,[5,6] François Lauzier MD MSc FRCPC,[1,7,8] Shane English MD MSc FRCPC,[9,11] Lynne Moore PhD,[1,12] Chartelin-Jean Isaac MSc, Alexis F. Turgeon MD MSc FRCPC

[1] CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada
[2] Department of Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[3] Department of Medical Oncology/Haematology & The Paul Albrechtsen Research Institute, CancerCare Winnipeg, Manitoba, Canada
[4] Centre for Experimental Medicine, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, Northern Ireland
[5] McGill University Health Centre, Montréal, Québec, Canada
[6] Peter Munk Cardiac Centre, Division of Cardiology and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada
[7] Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada
[8] Department of Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada
[9] Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
[10] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
[11] Department of Medicine, Division of Critical Care, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[12] Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada

Correspondence to: Dr. Alexis Turgeon, CHU de Québec — Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma-Emergency-Critical Care Medicine), 1401 18e rue, Québec City, QC, G1J 1Z4, Canada. Tel : +1 418-525-4444 ; email : alexis.turgeon@fmed.ulaval.ca

Short title: Statins in traumatic brain injury
Key words: Statins, traumatic brain injury, intervention, treatment, meta-analysis, review

Word count: 2338 words

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Background: Statins are considered a promising therapy in traumatic brain injury (TBI) because of their role at mediating inflammatory injury and other endothelial properties. Whether it can improve patient outcomes is unknown.

Objectives: To evaluate the effect of statins in critically ill patients with traumatic brain injury

Design: Systematic review and meta-analysis of randomized controlled trials

Eligibility criteria: Trials of adult patients with acute moderate or severe traumatic brain injury

Methods: We searched Medline, Embase, Cochrane Central and Web of Science databases for trials comparing the use of any statin with placebo or other interventions. Our primary outcome was the Glasgow Outcome Scale (GOS or GOSe); secondary outcomes were mortality, ICU and hospital length-of-stay. We used inverse variance random effect models to calculate risk ratios (RR) and weighted mean differences. We assessed the risk of bias of trials using the Cochrane risk of bias assessment tool and the presence of statistical heterogeneity using the I^2 index. Levels of evidence for summary effect measures were evaluated using GRADE methodology[1].

Results: Of 2,418 retrieved records, seven trials met our eligibility criteria. Three studied simvastatin and four studied atorvastatin. The duration of treatment ranged from 2 to 10 days and outcomes were assessed between ICU discharge and 6 months. Four trials were considered at high risk of bias. We observed no statistically significant association between statins and the Glasgow Outcome Scale (RR 0.42; 95% CI, 0.14–1.22; two trials; n=84, I^2=0%; very low certainty) or mortality (RR 0.59; 95% CI, 0.25–1.44; three trials; n=160, I^2=0%; very low certainty). No significant effect was observed for ICU length of stay while hospital length of stay was evaluated in one trial showing shorter duration.

Conclusion: We found no conclusive evidence supporting the use of statins in critically ill adult patients with TBI at this time. Nevertheless, trials were limited and confidence intervals wide. A potential benefit cannot be excluded supporting the role for a larger well-designed trial.

Registration: CRD42023421227

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Strengths and limitations of this study

- Our systematic review was designed to look at recommended patient-centered clinical outcomes to evaluate interventions in critically ill patients with TBI.
- Only randomized controlled trials were considered.
- Only a small number of trials were identified and the level of evidence of our findings is limited.
- Some registered trials are completed but still unpublished.

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Introduction

Traumatic brain injury (TBI) affects tens of millions of individuals worldwide each year and its incidence is increasing over time.[2,3] Despite major advances in our understanding of the disease, the optimal management of TBI patients remains uncertain, mainly focussing on preventing secondary cerebral injuries. Among the various treatment options, reducing oxidative stress has been considered one of the priorities.[4] Statins are among drug interventions that have been considered promising for their anti-inflammatory properties and other endothelial properties, independently of their low-density lipoprotein-cholesterol lowering effect.[5,6] Because they are readily available worldwide and relatively cheap, their use could easily be integrated into practice.

Nevertheless, evidence supporting their use in critically ill patients with TBI is unclear with preclinical studies showing promising results but clinical studies reporting conflicting ones.[7-13] Findings from previous systematic reviews are also conflicting,[14-21] which could be explained by differences in methods with the inclusion of non-randomized studies, TBI subpopulations, or in looking at the effect of the use of statins before the TBI.[15,19,22,23] Considering the potential mechanistic effect of statins, a clear understanding of their potential effect in the context of acute TBI is needed.

We therefore conducted a systematic review and meta-analysis of randomized controlled trials to assess the effect of statins on functional outcomes and mortality in the management of moderate to severe TBI.

Methods

Our systematic review was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews and Meta Analysis.[24] We registered the research protocol in the PROSPERO International prospective register of systematic reviews platform (Record ID: CRD42023421227) and reported our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes Guidelines (PRISMA).[25] Patients and public were not involved in this work.

Search Strategy

We systematically searched Medline (PubMed), Embase, Cochrane Central Register of Controlled Trials and Web of Science databases from their inception to March 2023 for eligible studies. The search strategy was designed with the help of an information specialist using the PRESS guidelines[26]. We identified trials

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using validated strategies to identify randomized controlled trials in Medline and Embase[27,28]. The strategy used for Web of Science was adapted from the Cochrane Ears, Nose, and Throat Disorder group[29]. The MEDLINE search strategy is presented in Appendix 1. We also conducted backward (by reviewing the reference list of included trials) and forward (by finding trials that cited included trials) citation searching to retrieve any additional relevant publications. In addition, we searched for ongoing and unpublished clinical trials in http://www.clinicaltrials.gov and http://www.controlled-trials.com registries.

Eligibility Criteria

Randomized controlled trials comparing the use of statins to any comparator (placebo, other intervention or no intervention) in critically ill adult patients (18 years or older) with acute moderate to severe TBI (defined as a Glasgow Coma Scale (GCS) score of 13 or less) were considered for eligibility. We included trials reporting at least one of our outcomes of interest. We considered trials if at least 80% of the study population was 18 years or older and suffered from a moderate to severe TBI. No language restriction was applied.

Study Selection and Data Extraction

Citations were reviewed independently by two reviewers (C.V. and C.J.I.) for eligibility. The same two reviewers independently extracted data using a standardized, pre-tested data extraction form. Disagreements were resolved by discussion leading to consensus, or by a third reviewer (A.F.T.). Following the completion of the screening, the AI tool of DistillerSR™ was used to verify for screening errors.

Retrieved information included characteristics of trials (design, number of participating centres, countries, group sizes), patient characteristics (including initial GCS score), intervention (type of statin, duration, and dosage regimen), controls, and outcomes. Screening and data extraction were completed using DistillerSR. Version 2.35. (DistillerSR Inc.; 2023, accessed March-December 2023, https://www.distillersr.com/).

Outcome measures

Our primary outcome was the Glasgow Outcome Scale (GOS) or the extended Glasgow Outcome Scale (GOSe) score.[30] We used the common definition of an unfavourable outcome (GOS 1-3 or GOSe 1-4).

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Secondary outcomes were mortality, intensive care unit (ICU) and hospital length of stay. When multiple assessments over time were reported, we used the latest reported one for our analysis.

Risk of bias assessment

The risk of bias of included trials was assessed independently by two reviewers (C.V. and C.J.I.) using the Cochrane Risk of Bias (RoB) 2 tool.[31] Disagreements were resolved through discussions leading to consensus, or by a third reviewer if disagreement persisted (A.F.T.). Trials were categorized as low, unclear, or high risk of bias based on the worst score obtained across the six domains.

Statistical Analyses

With Review Manager (RevMan) [version 5.4.1 The Cochrane Collaboration, 2020], we used random-effect models with the inverse variance method to calculate risk ratios (RR) for dichotomous outcomes and weighted mean differences (WMD) for continuous outcomes, with associated 95% confidence intervals (CI). When needed, we converted medians into means using previously described methods.[32,33] We evaluated the presence of statistical heterogeneity using the I^2 index.[34] We planned subgroup analyses based on TBI severity, presence (or not) of extra-cranial injury (isolated vs. multi-system trauma), type of statins (lipophilic vs. hydrophilic), dosage regimen, duration of the intervention and risk of bias of trials. We based the definition of dosage regimens of statins (high vs. low) on AHA/ACC guidelines to manage cholesterol based on the potency of each different statins.[35] We combined the dosage regimen of statins considered to have low to moderate potency in the low dose category. We evaluated potential publication bias with funnel plots.

Certainty of Evidence and Strength of Recommendations

We evaluated the certainty of evidence and strength of recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method[1]. The final quality of evidence was classified as high, moderate, low, or very low for each clinical outcome. Two reviewers (C.V. and C.J.I.) performed the classification of GRADE independently. Disagreements were resolved through discussions leading to consensus, or by a third reviewer if the disagreement persisted (A.F.T.).

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Results

Our search strategy retrieved 2,418 citations from which we removed 155 duplicates. Two trials were initially retrieved in clinical registries and the full-texts were made available during the course of this review.[36,37] Forty-six publications were assessed for full-text eligibility (Figure 1). Among registered trials, two are mentioned to be completed but are still unpublished,[38,39] and one is ongoing[40]. Seven trials[36,37,41-45] involving a total of 336 patients were included in our analyses.

Characteristics of trials

Six of the seven included trials were single center. Publication date ranged from 2016 to 2023 (Table 1). Five were conducted in Iran[41-45] and two in Egypt[36,37]. Trials enrolled from 20 to 100 patients. Six trials considered patients with moderate and/or severe TBI [36,37,41-45] while one enrolled only patients with severe injuries[44]. Patients requiring a neurosurgical intervention were excluded in four trials[42-45]. Three trials excluded patients who were previously on statins[36,41,44]. Atorvastatin was used in four trials[36,42,43,45] and simvastatin in the other three,[37,41,44]. The duration of treatment was two days in one trial[36], seven days in another trial[37], ten days in three trials[42,44,45] and unreported or unclear in the remaining two.[41,43]

Five trials were deemed at high risk of bias[37,41,42,44], one at unclear risk[36,43] and one trial was deemed at low risk of bias[45]. In one trial, the duration of the intervention was not reported and the methodology was limited[41] In another trial, the intervention was discontinued and about one third of the study population was lost to follow up[42]. In one trial, patients who died during the study were excluded from the analysis and discrepancies in the data reported were observed.[44] Finally, in another trial, patients requiring mechanical ventilation at any point during the hospital stay were excluded from the final analysis.[37] Funnel plots were not used to explore potential publication bias because of the low number of trials included.

Data synthesis

Glasgow Outcome Scale (GOS)

The Glasgow Outcome Scale was reported in three trials,[37,42,45] representing 144 patients evaluated at 90 or 180 days. In two trials, Glasgow Outcome Scale (GOS) scores were presented as proportions on the ordinal scale.[37,42] In another trial, the mean score of the GOS per group was reported[42]. Due to the impossibility to extract the number of patients with an unfavourable outcome per group, we could not

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include the data from this trial in our analyses. We found no statistically significant effect of statins on the Glasgow Outcome Scale (RR 0.42; 95% CI, 0.14–1.22; two trials; n = 84; I^2=0%; very low certainty) (Figure 3). The limited number of trials precluded our ability to conduct subgroup analyses.

Mortality

Data on mortality was available in five trials[37,42-45] with a follow-up of 14 to 180 days. Since no death occurred in two of the five trials, the data of those trials could not be included in the analysis. We observed no statistically significant effect of statins on mortality (RR, 0.59; 95% CI, 0.25–1.44; three trials; n = 160; I^2=0%; very low certainty) (Figure 4). No statistically significant effect was observed on mortality for statin dosage regimen, duration of intervention or risk of bias (Figure 5). Other planned subgroup analyses were not performed due to the limited information provided.

ICU and Hospital Length of Stay

Data from six trials[36,37,41,43-45] were included in the analysis of ICU length of stay. We did not observe a statistically significant effect on ICU length of stay with the use of statins (RR, -1.01; 95 % CI, -2.31–0.28; six trials; n = 292; I^2=74%; very low certainty) (Figure 4). These results were not modified by the severity of the TBI, the dosage regimen, the duration of intervention or the risk of bias (Figure 6).

Only one trial reported hospital length of stay[45] showing a reduced hospital length of stay with the use of statins (WMD, -3.70; 95 % CI, -4.48, -2.92; one trial; n = 60; very low certainty) (Figure 4).

Discussion

In our systematic review evaluating the use of statins in critically ill patients with acute moderate to severe TBI, we did not observe a statistically significant effect of this intervention on neurological functional outcomes, mortality or ICU length of stay. These observations are however based on a limited number of trials, most at high or unclear risk of bias, leading to a very low certainty of evidence. Available data cannot exclude the existence of benefits on patients centered outcomes and individual trials all suggests likewise.

Our results are somewhat consistent with those from five previous systematic reviews in acute traumatic brain injury[14,15,19-21]. Nevertheless, previous reviews included non-randomized studies, namely retrospective and prospective cohort studies, which are study designs that could overestimate the potential

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effect of an intervention. In addition, previous reviews evaluated mortality as the primary outcome, which is not considered the gold standard in TBI research, as a significant proportion of survivors have an unfavorable outcome with severe neurological deficits. Using the Glasgow outcome scale as our main outcome allows the evaluation of both mortality and neurological function, an outcome that is patient-centered. The difference between our results and prior reviews thus likely reflects the paucity of trials and differences in the outcomes evaluated.

Statins have been studied in other neurocritically ill conditions including chronic subdural hematoma[23,46], subarachnoid hemorrhage[47,48] and stroke[49,50]. The effect of statins following chronic subdural showed no increased risk of recurrence in one[41] but an accelerated hematoma resorption, decreased recurrence risk and surgical requirement in the other[23]. A recent network meta-analysis also found lower odds of recurrence of chronic subdural hematoma with the use of statins.[46] Of note, all three reviews included non-randomized studies. Two systematic reviews in patients with aneurysmal subarachnoid hemorrhage showed a decreased risk of delayed cerebral ischemia with the use of statins. These reviews, however, showed inconsistent beneficial effect on mortality and no statistically significant difference on functional outcomes[47,48]. On the other hand, systematic reviews that investigated the effect of statins on the recurrence of ischemic stroke in at risk population observed a beneficial effect stroke.[49,50] Interestingly, the choice of outcomes assessed seemed to largely influence the results as in TBI patients. All reviews conducted in other neurocritically ill populations evaluated mortality as a long-term outcome, an imperfect surrogate outcome of long-term neurologic functional outcomes.

Our systematic review has several strengths. First, it was designed to look at recommended[30] patient-centered clinical outcomes to evaluate interventions in critically ill patients with TBI. Secondly, we considered only randomized controlled trials to limit potential biases and ensure the best level of evidence. Our review also has limitations, largely centred around the limitations of the available body of evidence. The small number of trials identified limits statistical inferences and the extent of analyses that could be performed. Despite a thorough review of the existing evidence, the level of evidence of our findings is limited. Two registered trials are completed but still unpublished. However, their small sample size is unlikely to affect significantly the current findings.

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The baseline mortality rates observed in the trials included in our review are intriguingly low compared to observational studies.[51-57] The application of inclusion/exclusion criteria related to clinical trial enrollment may partially explain the comparatively low mortality observed (Table 1). Our results must thus be interpreted considering the exclusion of patients with the most severe forms of TBI. The duration of the intervention observed in the trials included in our review, ranging from 2 to 10 days, can be considered short by some to appropriately evaluate the effect of statins in this setting. Yet, the main potential effect is likely to be in the first days when the neuroinflammation is at its peak.[58-60] Whether the optimal dosage regimen was used in the trials could also be questioned since data from cardiology studies suggest the maximal effect is obtained with maximal doses.

Conclusion

In the context of limited information to confidently guide clinical decision-making on the use of statins, we did not observe a statistically significant improvement in neurologic functional outcome in critically ill adult patients with acute moderate to severe TBI. The small number of trials along with the very low certainty of evidence preclude the ability to draw conclusions and recommendations in this specific patient population. A well-designed and adequately powered multicenter randomized trial evaluating the effect of statins in moderate to severe TBI patients is required.

Acknowledgments: R Zarychanski is supported by the Lyonel G. Israels Research Chair in Hematology, University of Manitoba. P Lawler, F Lauzier and L Moore are recipients of salary support Awards from the Fonds de Recherche du Québec-Santé (FRQS). AF Turgeon is the chairholder of the Canada Research Chair in Critical Care Neurology and Trauma.

Competing Interests: The authors declare no competing interests.

Funding: This work was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (CIHR) (#148443).

Data sharing: Not applicable.

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Table 1. Characteristics of included trials

Trials	Country, number of centers and of participants (N)	Inclusion criteria	Exclusion criteria	Initial GCS (mean ± SD)	Dosage regimen and duration	Control	Outcome measures	Timing of outcome assessment
Naghibi et al. 2016[41]	Iran Single centre N=44	Adults (older than 18 years) admitted to ICU with isolated TBI and not receiving NSAIDs, statins, or corticosteroids, had no allergy to statins, no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic, or renal disease	Sepsis during the first 72 hours of admission or did not survive the first 72 hours of admission	Intervention group : 6.6±2.5 Control group: 7.6±2.9	Simvastatin 80 mg on day 1 and 40 mg daily after Duration of therapy not mentioned	Placebo	Mortality, ICU length of stay, duration of mechanical ventilation	ICU
Farzanegan et al. 2017[42]	Iran Single centre N=64	18 to 75-year-old TBI patients with GCS 5–13 and brain contusion <30 ml on CT	Patients requiring surgery or with severe injuries to internal organs, GCS of 3 and 4, Marshall grade IV or V, severe confounding injuries to internal organs, spinal cord injury, penetrating brain injuries, renal or hepatic diseases, creatinine >2.5 mg/dl or hemodialysis, bilirubin >1.5 times normal, brain tumor, stroke, infections and previous craniotomy, pregnancy or breastfeeding, INR > 1.5 or history of coagulopathy or anticoagulants, contusions in brain stem, initial SBP < 90 mm Hg without respond to fluid resuscitation, contraindications of PO medication, treatment with other investigational agents	Intervention group : 9.3±2.5 Control group: 8.4±2.7	Atorvastatin 20 mg for 10 days	Placebo	Glasgow outcome scale extended and contusion volume, mortality	3 months
Soltani et al. 2020[43]	Iran Single centre N=60	18 to 50-year-old patients with isolated TBI, GCS 5–13 and	GCS of 3 and 4, needing surgical evacuation, spinal cord injury, renal or hepatic diseases,	Intervention group : 5.1 Control group: 5.3	Atorvastatin 40 mg daily during ICU stay	Placebo	Mortality, duration of mechanical ventilation,	ICU

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		brain contusion <30 ml on CT	brain tumors, stroke, previous craniotomy, INR >1.5, coagulopathy or anticoagulants before to admission, and baseline systolic BP < 90 mm Hg without responding to fluid administration				ICU length of stay,	
Shafiee et al.2021[44]	Iran Single centre N=98	18 to 60-year-old TBI patients with GCS <9, no allergy to statins, non-use of NSAIDs, corticosteroids, statins, no intracranial lesion requiring neurosurgical intervention, no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic, or renal diseases	Simultaneous injury to other organs that required surgical intervention, presence of sepsis during the first 72 hours of admission to hospital, and history of drug poisoning	Intervention group : 6.4±1.3 Control group: 6.4±1.3	Simvastatin 40 mg for 10 days	Placebo	Hospital mortality, duration of mechanical ventilation and ICU length of ICU and neurosurger y ward stay	30 days
Soltani et al. 2021[45]	Iran Single centre N=60	18 to 75-year-old patients with TBI, GCS 5–14 and brain hemorrhage 25 m l to 30 ml on CT referred to < 10 hours from injury	GCS of 3 and 4; Marshall IV or V, spinal cord injury; kidney or liver disease, creatinine > 2.5 mg/dL or patients on dialysis; brain tumor, stroke, infection, and craniotomy, pregnant and lactating women, patients with SBP < 90 mm Hg, anticoagulants within 7 days before hospitalization; contraindications to receiving oral medication	Intervention group : 8.6±3.2 Control group: 8.3±3.1	Atorvastati n 20 mg for 10 days	Placebo	Glasgow outcome scale, disability rating scale, mortality, ICU length of stay, hospital length of stay	3 months
Hassanin et al. 2023[37]	Egypt Single centre N=40	18 to 60-year-old acute TBI patients admitted to ICU	Patients with major organ dysfunction (renal, liver, cardiovascular), drug or alcohol abuse, allergy to statins, myopathies, pregnancy or lactation, life-threatening multiple trauma, psychiatric disorder, prior history of neurological illness, or any trauma	Intervention group : 9±0 Control group: 9.4±0.8	Simvastatin 60 mg on day 1 then 40 mg for a total of 7 days	Placebo	Glasgow outcome scale, mortality, ICU length of stay,	6 months

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			requiring surgery. Need for mechanical ventilation at any point during the trial					
Zarief Kamel et al. 2023[36]	Egypt Single center N=20	Adults with TBI admitted to the ICU, GSC 9-11	Pre-trial lipid lowering therapy, pre-trauma immunosuppressive, anti-inflammatory or antipsychotic medication, uncontrolled systemic disease	Intervention group : 12.5±1.72 Control group: 12.5±1.72 (GCS on ICU admission)	Atorvastatin 40 mg for 2 days	Placebo	ICU length of stay	30 days

GSC: Glasgow Coma Scale; ICU: Intensive care unit; TBI: Traumatic brain injury; CT: Computed tomography

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Table 2. GRADE assessment for the certainty of the evidence

Certainty assessment							Nb of patients		Effect		Certainty	Importance
Nb of trials	Trial design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Statin	Control	Relative (95% CI)	Absolute (95% CI)		
Glasgow Outcome Scale												
2	RCT	Very serious[1]	Not serious	Not serious	Serious[2]	None	4/41	11/43	RR 0.42 (0.14 to 1.22)	296 fewer per 1000 (from 123 fewer to 550 more)[3]	Very Low ⊕◯◯◯	Critical
Mortality												
3	RCT	Very serious[4]	Not serious	Not serious	Serious[5]	None	7/80	12/80	RR 0.59 (0.25 to 1.44)	129 fewer per 1000 (from 59 fewer to 265 more)[6]	Very Low ⊕◯◯◯	Critical
ICU length of stay												
6	RCT	Very serious[7]	Serious[8]	Not serious	Serious[9]	None	149	143		MD -1.01 (-2.31 to 0.28]	Very Low ⊕◯◯◯	Important
Hospital length of stay												
1	RCT	Not serious	N/A	Serious[10]	Serious[11]	None	30	30		MD -3.70 (-4.48 to -2.92)	Very Low ⊕◯◯◯	Important

[1] Both trials had high risk of bias.
[2] Large confidence intervals caused by small number of events and overall risk ratio overlapped no effect (RR = 0.42, 95% CI :0.14, 1.22).
[3] Using a 50% unfavorable GOS at 30 days
[4] 3 of 5 trials included in the meta-analysis for mortality had a high risk of bias.
[5] Large confidence intervals caused by small number of events and overall risk ratio overlapped no effect (RR = 0.59, 95% CI: 0.25, 1.44).
[6] Using a 10% mortality at 30 days
[7] 4 of 6 trials included in the meta-analysis for ICU length of stay had a high risk of bias.
[8] Considerable heterogeneity among included studies (I^2 = 74%) and subgroups did not account for this heterogeneity.
[9] Large confidence intervals caused by small number of events and overall mean difference overlapped no effect (MD = -1.01, 95% CI: -2.31, 0.28).
[10] Only one trial provided data regarding this outcome.
[11] Large confidence intervals caused by small number of participants and overall mean difference overlapped no effect (MD = -3.7, 95% CI: -4.48, 2.92).

Legend: CI: Confidence interval; RR: Risk ratio; MD: Mean difference

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Appendix 1. MEDLINE search strategies

((brain* [TIAB] AND injur*[TIAB]) OR (brain* [TIAB] AND traum* [TIAB]) OR (head* [TIAB] AND injur* [TIAB]) OR (head* [TIAB] AND traum*) OR (crani* [TIAB] AND injur* [TIAB]) OR (crani* AND traum* [TIAB]) OR (intracrani* and injur* [TIAB]) OR (intracrani* [TIAB] AND traum* [TIAB]) OR (intra-crani* [TIAB] AND injur* [TIAB]) OR (intra-crani* [TIAB] AND traum* [TIAB]) OR (cereb* [TIAB] AND injur* [TIAB]) OR (cereb* [TIAB] AND traum* [TIAB]) OR tbi [TIAB] OR concuss* [TIAB] OR (acute brain injuries[MeSH Terms]) OR (acute brain injury[MeSH Terms]) OR (brain injury[MeSH Terms]) OR (brain injuries[MeSH Terms]) OR (brain trauma[MeSH Terms]) OR (brain traumas[MeSH Terms]) OR (craniocerebral injury[MeSH Terms]) OR (craniocerebral injuries[MeSH Terms]) OR (craniocerebral trauma[MeSH Terms]) OR (craniocerebral traumas[MeSH Terms]) OR (diffuse axonal injury[MeSH Terms]) OR (diffuse axonal injuries[MeSH Terms]) OR (injury, diffuse axonal[MeSH Terms]) OR (injuries, diffuse axonal[MeSH Terms]) OR (closed head injury[MeSH Terms]) OR (closed head injuries[MeSH Terms]) OR (blunt head injury[MeSH Terms]) OR (blunt head injuries[MeSH Terms]) OR (coma, post head injury[MeSH Terms]) OR (intracranial hemorrhage, traumatic[MeSH Terms]) OR (hemorrhage, traumatic brain[MeSH Terms]) OR (trauma, nervous system[MeSH])) AND ((Hydroxymethylglutaryl-CoA Reductase Inhibitor*) OR (HMG CoA reductase inhibitor*) OR (hmg coenzyme a reductase inhibitor*) OR (hmg-coa reductase inhibitor*) OR (hydroxymethylglutaryl coa reductase inhibitor*) or (hydroxymethylglutaryl-coa reductase inhibitor*) OR (hmg coa statins[MeSH Terms]) OR (statins, hmg coa[MeSH Terms]) OR (statin*) OR (atorvastatin) OR (atorvaliq) OR (arkas) OR (ator) OR (atoris) OR (torvast) OR (totalip) OR (lipitor) OR (bervastatin) OR (cerivastatin) OR (baycol) OR (lipobay) OR (crilvastatin) OR (dalvastin) OR (fluvastatin) OR (lescol XL) OR (lescol) OR (lipaxan) OR (primesin) OR (fluindostatin) OR (glenvastatin) OR (lovastatin) OR (altoprev) OR (altocor) OR (mevacor) OR (monacolin) OR (mevinolin) OR (mevastatin) OR (compactin) OR (pravastatin) OR (aplactin) OR (lipostat) OR (prasterol) OR (pravachol) OR (pravaselect) OR (sanaprav) OR (selectin) OR (selektine) OR (vasticor) OR (pitavastatin) OR (alipza) OR (livalo) OR (livazo) OR (pitava) or (zypitamag) OR (rosuvatatin) OR (colcardiol) OR (colfri) OR (crativ) OR (crestor) OR (dilivas) OR (exorta) OR (ezallor) OR (koleros) OR (lipidover) OR (miastina) OR (provisacor) OR (rosastin) OR (simestat) OR (staros) OR (simvastatin) OR (alpheus) OR (flolipid) OR (krustat) OR (lipenil) OR (lipex) OR (liponorm) OR (medipo) OR (omistat) OR (rosim) OR (setorilin) OR (simbatrix) OR (sincol) OR (sinvacor) OR (sinvalip) OR (sivastin) OR (sinvat) OR (vastgen) OR (vastin) OR (xipocol) OR (zocor) OR (tenivastatin)) AND (randomized controlled trial [PT] OR controlled clinical trial [PT] OR randomized [TIAB] OR placebo [TIAB] OR drug therapy [SH] OR randomly [TIAB] OR trial [TIAB] OR groups [TIAB] NOT (animals [MH] NOT humans [MH]))

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Figure 1. Flow diagram of trials

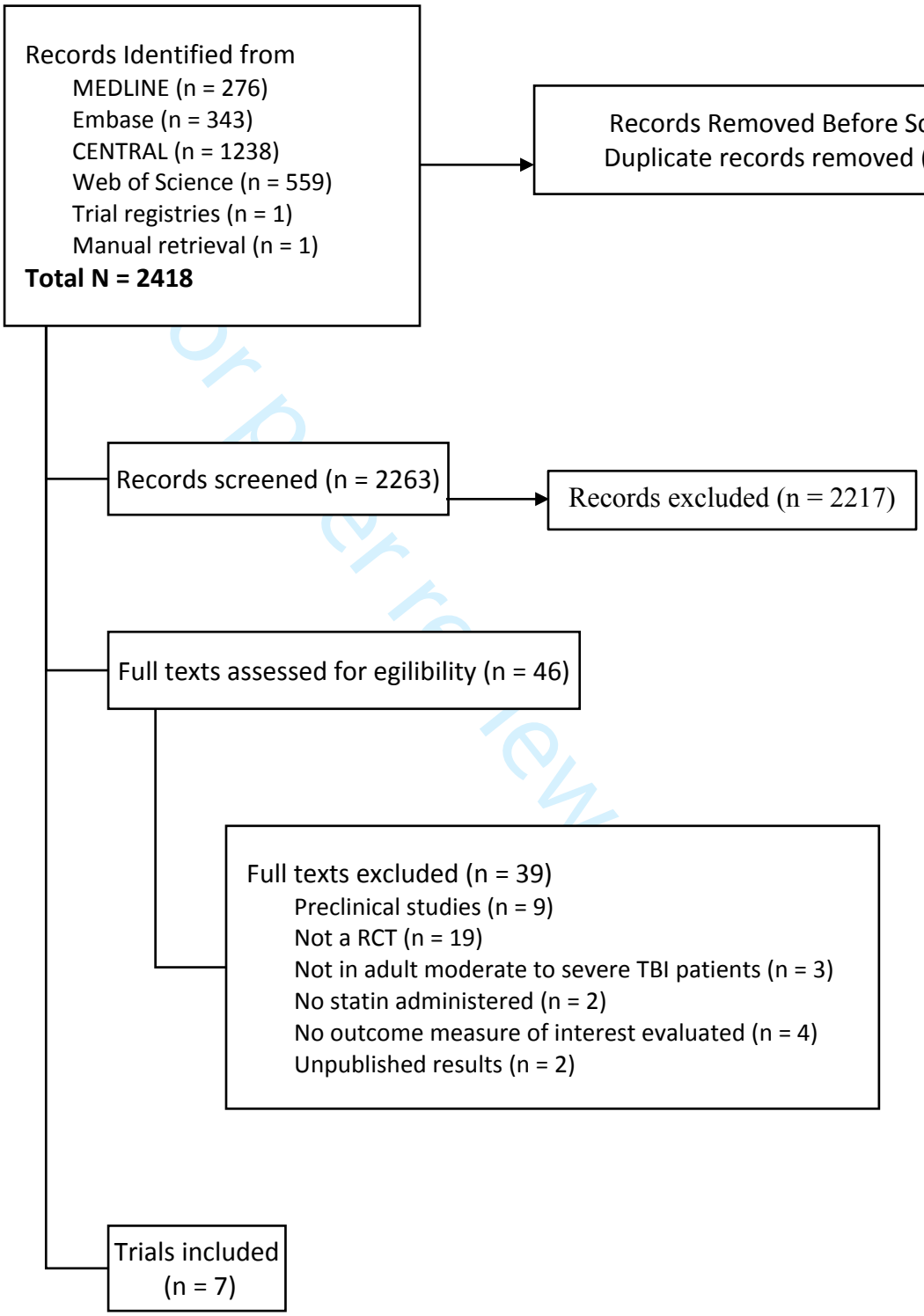

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Figure 1. Risk of bias of trials

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Figure 3. Effect of statins on the incidence of unfavourable neurological functional outcomes (Glasgow Outcome Scale)

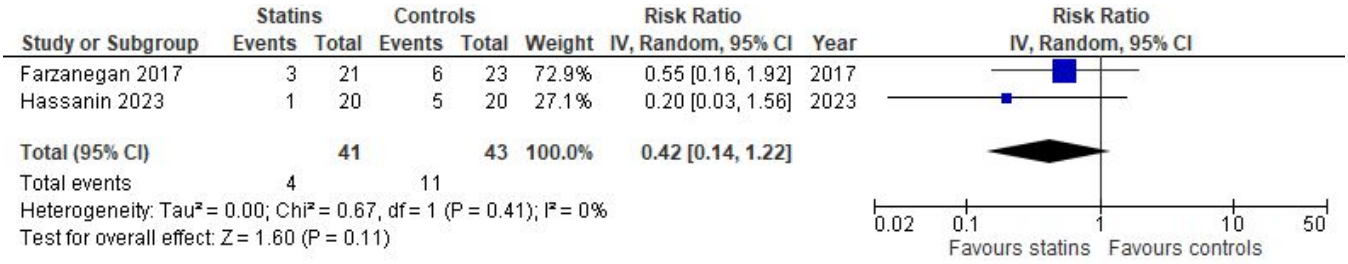

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Figure 4. Secondary outcomes

Outcomes	Nbr of trials	Nbr of participants	Measure of association	Summary of Effect [95% CI]	I^2	Certainty of the evidence
Mortality	3	160	Risk ratio	0.59 [0.25, 1.44]	0%	Very low
Length of ICU stay	6	292	WMD* (days)	-1.01 [-2.31, 0.28]	74%	Very low
Length of hospital stay	1	60	WMD* (days)	-3.70 [-4.48, -2.92]	N/A	Very low

*WMD: Weighted Mean Difference. Random effects models with the inverse variance were used for all analyses

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Figure 5. Subgroup analyses of mortality

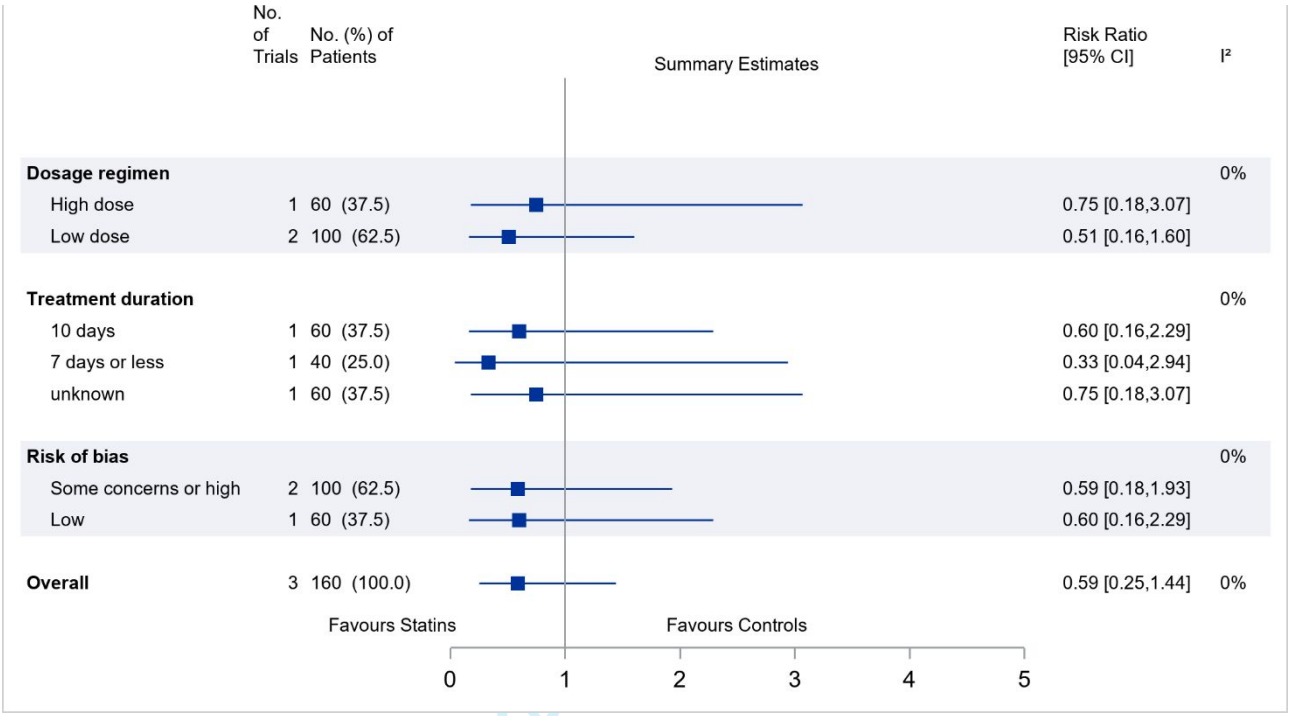

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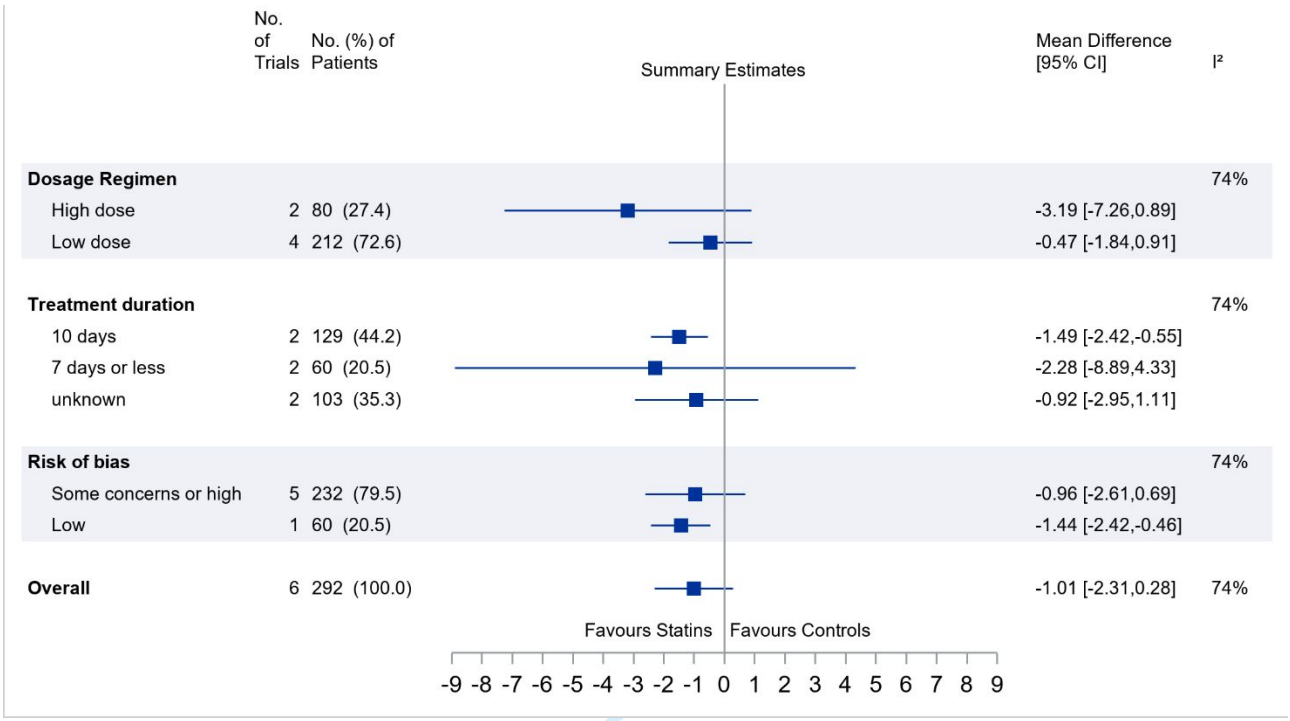
Figure 6. Subgroup analyses of ICU length of stay



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BMJ Open

Effect of statins on neurologic functional outcomes in critically ill adult patients with traumatic brain injury: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091971.R1
Article Type:	Original research
Date Submitted by the Author:	01-Feb-2025

Complete List of Authors:	Veillette, Charles; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada Umana, Mauricio; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada Gagnon, Marc-Aurèle; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Costerousse, Olivier ; Centre de recherche du CHU de Québec-Université Laval, Population Health and Optimal Practices Zarychanski, Ryan ; University of Manitoba, Sections of Critical Care and Hematology/Medical Oncology McAuley, Daniel; Queen's University Belfast, Centre for Experimental Medicine Lawler, Patrick; McGill University Health Centre; University Health Network Lauzier, Francois; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, é English, Shane; Ottawa Hospital Research Institute, Clinical Epidemiology Program; University of Ottawa, Division of Critical Care, Department of Medicine Moore, Lynne; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Isaac, Chartelin-Jean; CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada, Turgeon, Alexis; Centre de recherche du CHU de Quebec-Universite Laval Site CHUL, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine)

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Neurology
Keywords:	Brain Injuries, Drug Therapy, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurological injury < NEUROLOGY, Systematic Review

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Effect of statins on neurologic functional outcomes in critically ill adult patients with traumatic brain injury: A systematic review and meta-analysis

Charles Veillette MD FRCPC,[1] Mauricio Umana MD,[1] Marc-Aurèle Gagnon MSc,[1] Olivier Costerousse PhD,[1] Ryan Zarychanski MD MSc FRCPC,[2,3] Danny McAuley MD,[4] Patrick Lawler MD MSc FRCPC,[5,6] François Lauzier MD MSc FRCPC,[1,7,8] Shane English MD MSc FRCPC,[9,11] Lynne Moore PhD,[1,12] Chartelin-Jean Isaac MSc[1], Alexis F. Turgeon MD MSc FRCPC[1,7]

[1] CHU de Québec – Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma – Emergency – Critical Care Medicine), Université Laval, Québec City, Québec, Canada
[2] Department of Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[3] Department of Medical Oncology/Haematology & The Paul Albrechtsen Research Institute, CancerCare Winnipeg, Manitoba, Canada
[4] Centre for Experimental Medicine, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, Northern Ireland
[5] McGill University Health Centre, Montréal, Québec, Canada
[6] Peter Munk Cardiac Centre, Division of Cardiology and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada
[7] Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada
[8] Department of Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada
[9] Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
[10] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
[11] Department of Medicine, Division of Critical Care, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[12] Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada

Correspondence to: Dr. Alexis Turgeon, CHU de Québec — Université Laval Research Center, Population Health and Optimal Health Practices Research Unit (Trauma-Emergency-Critical Care Medicine), 1401 18e rue, Québec City, QC, G1J 1Z4, Canada. Tel : +1 418-525-4444 ; email : alexis.turgeon@fmed.ulaval.ca

Short title: Statins in traumatic brain injury
Key words: Statins, traumatic brain injury, intervention, treatment, meta-analysis, review

Word count: 2504 words

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Background: Statins are considered a promising therapy in traumatic brain injury (TBI) because of their role at mediating inflammatory injury and other endothelial properties. Whether it can improve patient outcomes is unknown.

Objectives: To evaluate the effect of statins in critically ill patients with traumatic brain injury

Design: Systematic review and meta-analysis of randomized controlled trials

Eligibility criteria: Trials of adult patients with acute moderate or severe traumatic brain injury

Methods: We searched Medline, Embase, Cochrane Central and Web of Science databases for trials comparing the use of any statin with placebo or other interventions. Our primary outcome was the Glasgow Outcome Scale (GOS or GOSe); secondary outcomes were mortality, ICU and hospital length-of-stay. We used inverse variance random effect models to calculate risk ratios (RR) and weighted mean differences. We assessed the risk of bias of trials using the Cochrane risk of bias assessment tool and the presence of statistical heterogeneity using the I^2 index. Levels of evidence for summary effect measures were evaluated using GRADE methodology[1].

Results: Of 2,418 retrieved records, seven trials met our eligibility criteria. Three studied simvastatin and four studied atorvastatin. The duration of the intervention ranged from 2 to 10 days and outcomes were assessed between ICU discharge and 6 months. Five trials were considered at high risk of bias. We observed no statistically significant association between statins and the Glasgow Outcome Scale (RR 0.42; 95% CI, 0.14–1.22; two trials; n=84, I^2=0%; very low certainty) or mortality (RR 0.59; 95% CI, 0.25–1.44; three trials; n=160, I^2=0%; very low certainty). No significant effect was observed for ICU length of stay while hospital length of stay was evaluated in one trial showing shorter duration.

Conclusion: We found no conclusive evidence supporting the use of statins in critically ill adult patients with TBI at this time. Nevertheless, the trials were limited and wide confidence intervals resulted in significant uncertainty of the findings. A potential benefit cannot be rulled-out, underscoring the need for a larger, well-designed trial.

Registration: CRD42023421227

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Strengths and limitations of this study

- Our systematic review was designed to look at recommended patient-centered clinical outcomes to evaluate interventions in critically ill patients with TBI.
- Only randomized controlled trials were considered.
- Only a small number of trials were identified and the level of evidence of our findings is limited.
- Some registered trials are completed but still unpublished.

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Introduction

Traumatic brain injury (TBI) affects tens of millions of individuals worldwide each year and its incidence is increasing over time.[2,3] Despite major advances in our understanding of the disease, the optimal management of TBI patients remains uncertain, mainly focussing on preventing secondary cerebral injuries. Among the various treatment options, reducing oxidative stress has been considered one of the priorities.[4] Statins are among drug interventions that have been considered promising for their anti-inflammatory properties and other endothelial properties, independently of their low-density lipoprotein-cholesterol lowering effect.[5,6] Because they are readily available worldwide and relatively cheap, their use could easily be integrated into practice.

Nevertheless, evidence supporting their use in critically ill patients with TBI is unclear with preclinical studies showing promising results but clinical studies reporting conflicting ones.[7-13] Findings from previous systematic reviews are also conflicting,[14-21] which could be explained by differences in methods with the inclusion of non-randomized studies, TBI subpopulations, or in looking at the effect of the use of statins before the TBI.[15,19,21,22] Considering the potential mechanistic effect of statins, a clear understanding of their potential effect in the context of acute TBI is needed.

We therefore conducted a systematic review and meta-analysis of randomized controlled trials to assess the effect of statins on functional outcomes and mortality in the management of moderate to severe TBI.

Methods

Our systematic review was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews and Meta Analysis.[23] We registered the research protocol in the PROSPERO International prospective register of systematic reviews platform (Record ID: CRD42023421227) and reported our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes Guidelines (PRISMA).[24] Patients and public were not involved in this work.

Search Strategy

We systematically searched Medline (PubMed), Embase, Cochrane Central Register of Controlled Trials and Web of Science databases from their inception to March 2023 for eligible studies. The search strategy was designed with the help of an information specialist using the PRESS guidelines[25]. We identified trials using validated strategies to identify randomized controlled trials in Medline and Embase[26,27]. The strategy

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used for Web of Science was adapted from the Cochrane Ears, Nose, and Throat Disorder group[28]. The MEDLINE search strategy is presented in Appendix 1. We also conducted backward (by reviewing the reference list of included trials) and forward (by finding trials that cited included trials) citation searching to retrieve any additional relevant publications. In addition, we searched for ongoing and unpublished clinical trials in http://www.clinicaltrials.gov and http://www.controlled-trials.com registries.

Eligibility Criteria

Randomized controlled trials comparing the use of statins to any comparator (placebo, other intervention or no intervention) in critically ill adult patients (18 years or older) with acute moderate to severe TBI (defined as a Glasgow Coma Scale (GCS) score of 13 or less) were considered for eligibility. We included trials reporting at least one of our outcomes of interest. We considered trials if at least 80% of the study population was 18 years or older and suffered from a moderate to severe TBI. No language restriction was applied.

Study Selection and Data Extraction

Citations were reviewed independently by two reviewers (C.V. and C.J.I.) for eligibility. The same two reviewers independently extracted data using a standardized, pre-tested data extraction form. Disagreements were resolved by discussion leading to consensus, or by a third reviewer (A.F.T.). Following the completion of the screening, the AI tool of DistillerSR™ was used to verify for screening errors.

Retrieved information included characteristics of trials (design, number of participating centres, countries, group sizes), patient characteristics (including initial GCS score), intervention (type of statin, duration, and dosage regimen), controls, and outcomes. Screening and data extraction were completed using DistillerSR. Version 2.35. (DistillerSR Inc.; 2023, accessed March-December 2023, https://www.distillersr.com/).

Outcome measures

Our primary outcome was the Glasgow Outcome Scale (GOS) or the extended Glasgow Outcome Scale (GOSe) score.[29-31] The GOS is a 5-point ordinal scale while the GOSe is an updated version on 8 points. A GOS or a GOSe of 1 corresponding to death and a GOS of 5 or a GOSe of 8 corresponding to a full recovery. We used the common definition of an unfavourable outcome (GOS 1-3 or GOSe 1-4). Secondary

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outcomes were mortality, intensive care unit (ICU) and hospital length of stay. When multiple assessments over time were reported, we used the latest reported one for our analysis.

Risk of bias assessment

The risk of bias of included trials was assessed independently by two reviewers (C.V. and C.J.I.) using the Cochrane Risk of Bias (RoB) 2 tool. Disagreements were resolved through discussions leading to consensus, or by a third reviewer if disagreement persisted (A.F.T.). Trials were categorized as low, unclear, or high risk of bias based on the worst score obtained across the six domains.

Statistical Analyses

With Review Manager (RevMan) [version 5.4.1 The Cochrane Collaboration, 2020], we used random-effect models with the inverse variance method to calculate risk ratios (RR) for dichotomous outcomes and weighted mean differences (WMD) for continuous outcomes, with associated 95% confidence intervals (CI). When needed, we converted medians into means using previously described methods. [33,34] We evaluated the presence of statistical heterogeneity using the I^2 index. [35] We planned subgroup analyses based on TBI severity, presence (or not) of extra-cranial injury (isolated vs. multi-system trauma), type of statins (lipophilic vs. hydrophilic), dosage regimen, duration of the intervention and risk of bias of trials. We based the definition of dosage regimens of statins (high vs. low) on AHA/ACC guidelines to manage cholesterol based on the potency of each different statins.[36] We combined the dosage regimen of statins considered to have low to moderate potency in the low dose category. We evaluated potential publication bias with funnel plots.

Certainty of Evidence and Strength of Recommendations

We evaluated the certainty of evidence and strength of recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method[1]. The final quality of evidence was classified as high, moderate, low, or very low for each clinical outcome. Two reviewers (C.V. and C.J.I.) performed the classification of GRADE independently. Disagreements were resolved through discussions leading to consensus, or by a third reviewer if the disagreement persisted (A.F.T.).

Results

Our search strategy retrieved 2,418 citations from which we removed 155 duplicates. Two trials were initially retrieved in clinical registries and the full-texts were made available during the course of this

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review.[37,38] Forty-six publications were assessed for full-text eligibility (Figure 1). Among registered trials, two are mentioned to be completed but are still unpublished,[39,40] and one is ongoing[41]. Seven trials[37,38,42-46] involving a total of 336 patients were included in our analyses.

Characteristics of trials

Six of the seven included trials were single center. Publication date ranged from 2016 to 2023 (eTable 1). Five were conducted in Iran[42-46] and two in Egypt[37,38]. Trials enrolled from 20 to 100 patients. Six trials considered patients with moderate and/or severe TBI[37,38,42-46] while one enrolled only patients with severe injuries[45]. Patients requiring a neurosurgical intervention were excluded in four trials[43-46]. Three trials excluded patients who were previously on statins[37,42,45]. Atorvastatin was used in four trials[37,43,44,46] and simvastatin in the other three[38,42,45]. The duration of treatment was two days in one trial[37], seven days in another trial[38], ten days in three trials[43,45,46] and unreported or unclear in the remaining two. [42,44]

Five trials were deemed at high risk of bias[38,42,43,44], one at unclear risk[37,44] and one trial was deemed at low risk of bias[46] (Figure 2). In one trial, the duration of the intervention was not reported and the methodology was limited[42] In another trial, the intervention was discontinued and about one third of the study population was lost to follow up[41]. In one trial, patients who died during the study were excluded from the analysis and discrepancies in the data reported were observed.[45] Finally, in another trial, patients requiring mechanical ventilation at any point during the hospital stay were excluded from the final analysis.[38] Funnel plots were not used to explore potential publication bias because of the low number of trials included.

Data synthesis

Glasgow Outcome Scale (GOS)

The Glasgow Outcome Scale was reported in three trials,[38,43,46] representing 144 patients evaluated at 90 or 180 days. In two trials, Glasgow Outcome Scale (GOS) scores were presented as proportions on the ordinal scale.[38,43] In another trial, the mean score of the GOS per group was reported[43]. Due to the impossibility to extract the number of patients with an unfavourable outcome per group, we could not include the data from this trial in our analyses. We found no statistically significant effect of statins on the Glasgow Outcome Scale (RR 0.42; 95% CI, 0.14–1.22; two trials; n = 84; I^2=0%; very low certainty) (Figure 3, eTable 2). The limited number of trials precluded our ability to conduct subgroup analyses.

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Mortality

Data on mortality was available in five trials[38,43,46] with a follow-up of 14 to 180 days. Since no death occurred in two of the five trials, the data of those trials could not be included in the analysis. We observed no statistically significant effect of statins on mortality (RR, 0.59; 95% CI, 0.25–1.44; three trials; n = 160; I^2=0%; very low certainty) (Figure 4) (Figure 5). No statistically significant effect was observed on mortality for statin dosage regimen, duration of intervention or risk of bias (Figure 6, eTable 2). Other planned subgroup analyses were not performed due to the limited information provided.

ICU and Hospital Length of Stay

Data from six trials[37,38,42,44,46] were included in the analysis of ICU length of stay. We did not observe a statistically significant effect on ICU length of stay with the use of statins (RR, -1.01; 95 % CI, -2.31–0.28; six trials; n = 292; I^2=74%; very low certainty) (Figure 5). These results were not modified by the severity of the TBI, the dosage regimen, the duration of intervention or the risk of bias.

Only one trial reported hospital length of stay[46] showing a reduced hospital length of stay with the use of statins (WMD, -3.70; 95 % CI, -4.48, -2.92; one trial; n = 60; very low certainty) (Figure 5, eTable 2).

Discussion

In our systematic review evaluating the use of statins in critically ill patients with acute moderate to severe TBI, we did not observe a statistically significant effect of this intervention on neurological functional outcomes, mortality, or ICU length of stay. These observations are however based on a limited number of trials, most at high or unclear risk of bias, leading to a very low certainty of evidence. Available data cannot exclude the existence of benefits on patients-centered outcomes and individual trials all suggest likewise.

Our results are somewhat consistent with those from five previous systematic reviews in acute traumatic brain injury since most concluded that statins might be beneficials in TBI patients[14,15,19-21]. Nevertheless, these reviews included non-randomized studies, namely retrospective and prospective cohort studies, which are study designs that could overestimate the potential effect of an intervention. In addition, some of the previous reviews evaluated mortality as the primary outcome, which is not considered the gold standard in TBI research, as a significant proportion of survivors have an unfavorable outcome with severe

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neurological deficits. Other reviews based their conclusion on laboratory results which may not be clinically significant and not patient-centered outcomes. Using the Glasgow Outcome Scale as our main outcome allows the evaluation of both mortality and neurological function, an outcome that is patient-centered. The difference between our results and prior reviews thus likely reflects the paucity of trials and differences in the outcomes evaluated.

Statins have been studied in other neurocritically ill conditions including chronic subdural hematoma[22,47], subarachnoid hemorrhage[48,49] and stroke[50,51]. The effect of statins following chronic subdural showed no increased risk of recurrence in one[42] but an accelerated hematoma resorption, decreased recurrence risk and surgical requirement in the other[22]. A recent network meta-analysis also found lower odds of recurrence of chronic subdural hematoma with the use of statins.[47] Of note, all three reviews included non-randomized studies. Two systematic reviews in patients with aneurysmal subarachnoid hemorrhage showed a decreased risk of delayed cerebral ischemia with the use of statins. These reviews, however, showed inconsistent beneficial effect on mortality and no statistically significant difference on functional outcomes[48,49]. On the other hand, systematic reviews that investigated the effect of statins on the recurrence of ischemic stroke in at risk population observed a beneficial effect.[50,51] Interestingly, the choice of outcomes assessed seemed to largely influence the results as in TBI patients. All reviews conducted in other neurocritically ill populations evaluated mortality as a long-term outcome, an imperfect surrogate outcome of long-term neurologic functional outcomes.

Trials focusing on mild TBI were excluded since their population is largely different from moderate to severe TBI patients. These patients often don't require hospital admission and almost never require hospitalisation in the intensive care unit. Although they can present long term symptoms, there evolution is favorable with at most minor disabilities. Therefore, study results including this subtype of patients would not inform clinicians about the management of critical ill TBI patients.

Our systematic review has several strengths. First, it was designed to look at recommended29 patient-centered clinical outcomes to evaluate interventions in critically ill patients with TBI. Secondly, we considered only randomized controlled trials to limit potential biases and ensure the best level of evidence. Our review also has limitations, largely centred around the limitations of the available body of evidence. The small number of trials identified limits statistical inferences and the extent of analyses that could be performed. Despite a thorough review of the existing evidence, the level of evidence of our findings is

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limited. Two registered trials are completed but still unpublished (NCT05551871, IRCT201109197595). However, their small sample size is unlikely to significantly affect the current findings.

The baseline mortality rates observed in the trials included in our review are intriguingly low compared to observational studies.[52-58] The application of inclusion/exclusion criteria related to clinical trial enrollment may partially explain the comparatively low mortality observed. Our results must thus be interpreted considering the exclusion of patients with the most severe forms of TBI. The duration of the intervention observed in the trials included in our review, ranging from 2 to 10 days, can be considered short by some to appropriately evaluate the effect of statins in this setting. Yet, the main potential effect is likely to be in the first days when the neuroinflammation is at its peak.[59-61] Furthermore, the dosage regimens that were used in the trials could also be questioned, as data from studies in other patient populations suggest that the optimal effect is achieved with the highest doses.[62,63]

Conclusion

We did not observe a statistically significant improvement in neurologic functional outcome in critically ill adult patients with acute moderate to severe TBI. This observation relies on scant data and trials presenting significant risks of biases and therefore, cannot confidently guide clinical decision making. The small number of trials along with the very low certainty of evidence preclude the ability to draw conclusions and recommendations in this specific patient population. A well-designed and adequately powered multicenter randomized trial evaluating the effect of statins in moderate to severe TBI patients is required.

Acknowledgments: R Zarychanski is supported by the Lyonel G. Israels Research Chair in Hematology, University of Manitoba. P Lawler, F Lauzier and L Moore are recipients of salary support Awards from the Fonds de Recherche du Québec-Santé (FRQS). AF Turgeon is the chairholder of the Canada Research Chair in Critical Care Neurology and Trauma.

Competing Interests: The authors declare no competing interests.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Authors contribution : Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (CV, MU, MAG, OC, RZ, DM, PL, FL, SE, LM, CJI, AFT); AND Drafting the work (CV, MU, MAG, OC, AFT) or revising it critically for important intellectual content (CV, MU, MAG, OC, RZ, DM, PL, FL, SE, LM, CJI, AFT); AND Final approval of the version to be published (CV, MU, MAG, OC, RZ, DM, PL, FL, SE, LM, CJI, AFT); AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (CV, MU, MAG, OC, RZ, DM, PL, FL, SE, LM, CJI, AFT). Alexis F. Turgeon is the guarantor

Funding: This work was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (CIHR) (#148443).

Data sharing: Not applicable.

Figure legends

Figure 1. Flow diagram of trials

Figure 2. Risk of bias of trials

Figure 3. Effect of statins on the incidence of unfavourable neurologic functional outcomes (Glasgow Outcome Scale)

Figure 4. Effect of statins on mortality

Figure 5. Secondary outcomes

Figure 6. Subgroup analyses of mortality

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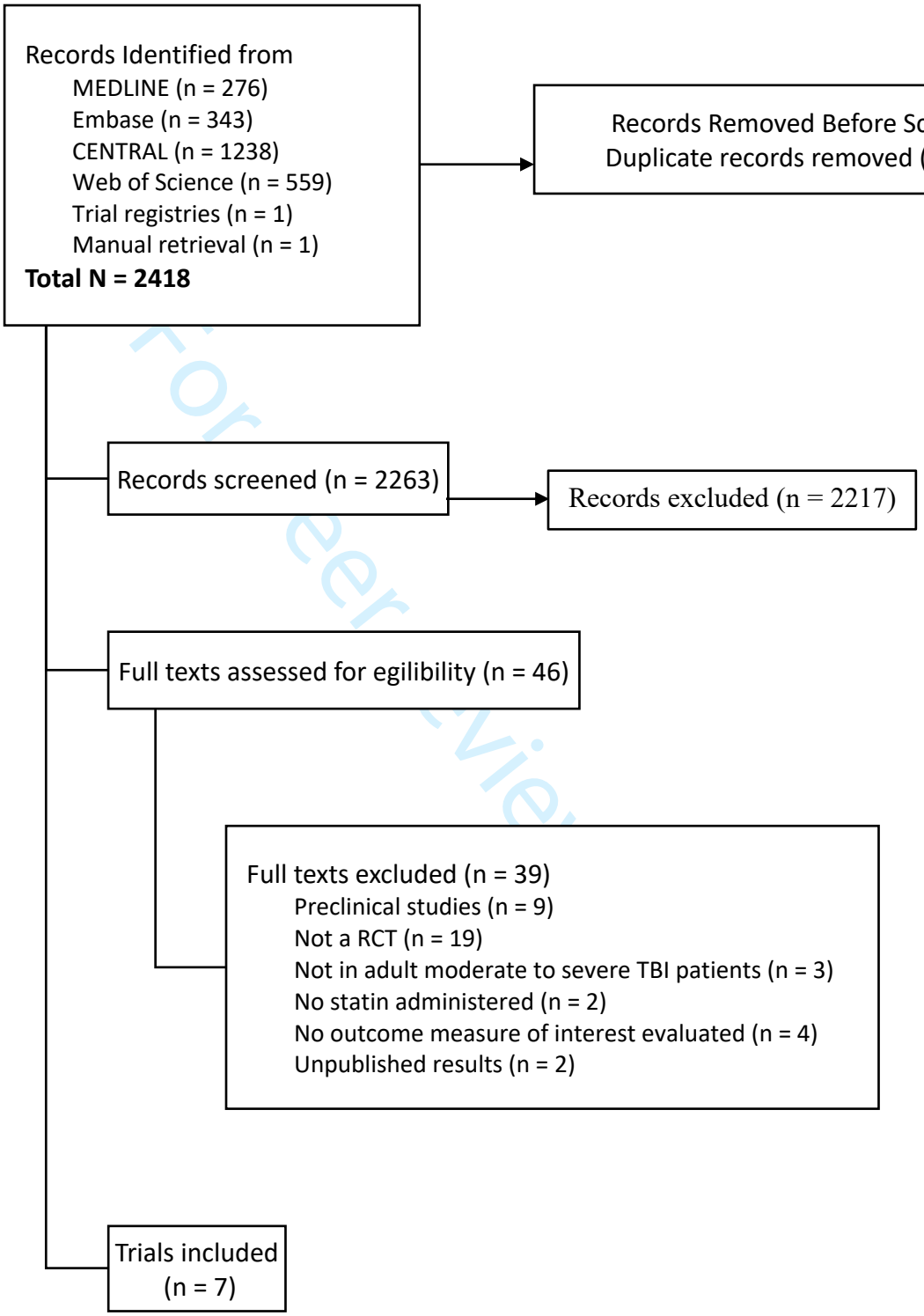

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Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.

Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

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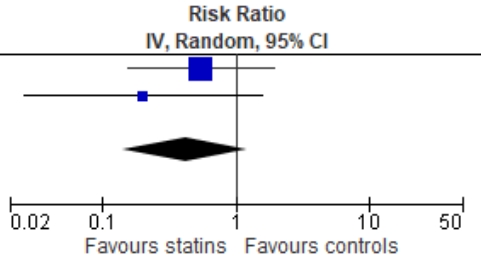
Study or Subgroup	Statins Events	Total	Controls Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Farzanegan 2017	3	21	6	23	72.9%	0.55 [0.16, 1.92]	2017
Hassanin 2023	1	20	5	20	27.1%	0.20 [0.03, 1.56]	2023
Total (95% CI)		**41**		**43**	**100.0%**	**0.42 [0.14, 1.22]**	
Total events	4		11				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$

Test for overall effect: Z = 1.60 (P = 0.11)



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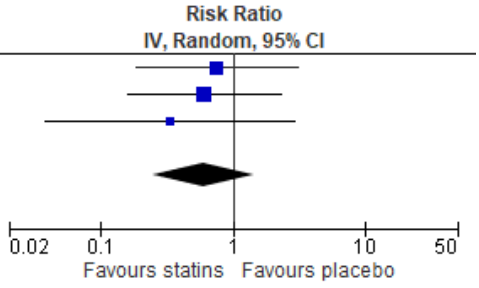
Study or Subgroup	Statins Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Soltani 2020	3	30	4	30	39.6%	0.75 [0.18, 3.07]	2020
Soltani 2021	3	30	5	30	43.8%	0.60 [0.16, 2.29]	2021
Hassanin 2023	1	20	3	20	16.6%	0.33 [0.04, 2.94]	2023
Total (95% CI)		**80**		**80**	**100.0%**	**0.59 [0.25, 1.44]**	
Total events	7		12				

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%

Test for overall effect: Z = 1.15 (P = 0.25)



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Outcomes	Nbr of trials	Nbr of participants	Measure of association	Summary of Effect [95% CI]	I^2	Certainty of the evidence
Mortality	3	160	Risk ratio	0.59 [0.25, 1.44]	0%	Very low
Length of ICU stay	6	292	WMD* (days)	-1.01 [-2.31, 0.28]	74%	Very low
Length of hospital stay	1	60	WMD* (days)	-3.70 [-4.48, -2.92]	N/A	Very low

*WMD: Weighted Mean Difference. Random effects models with the inverse variance were used for all analyses

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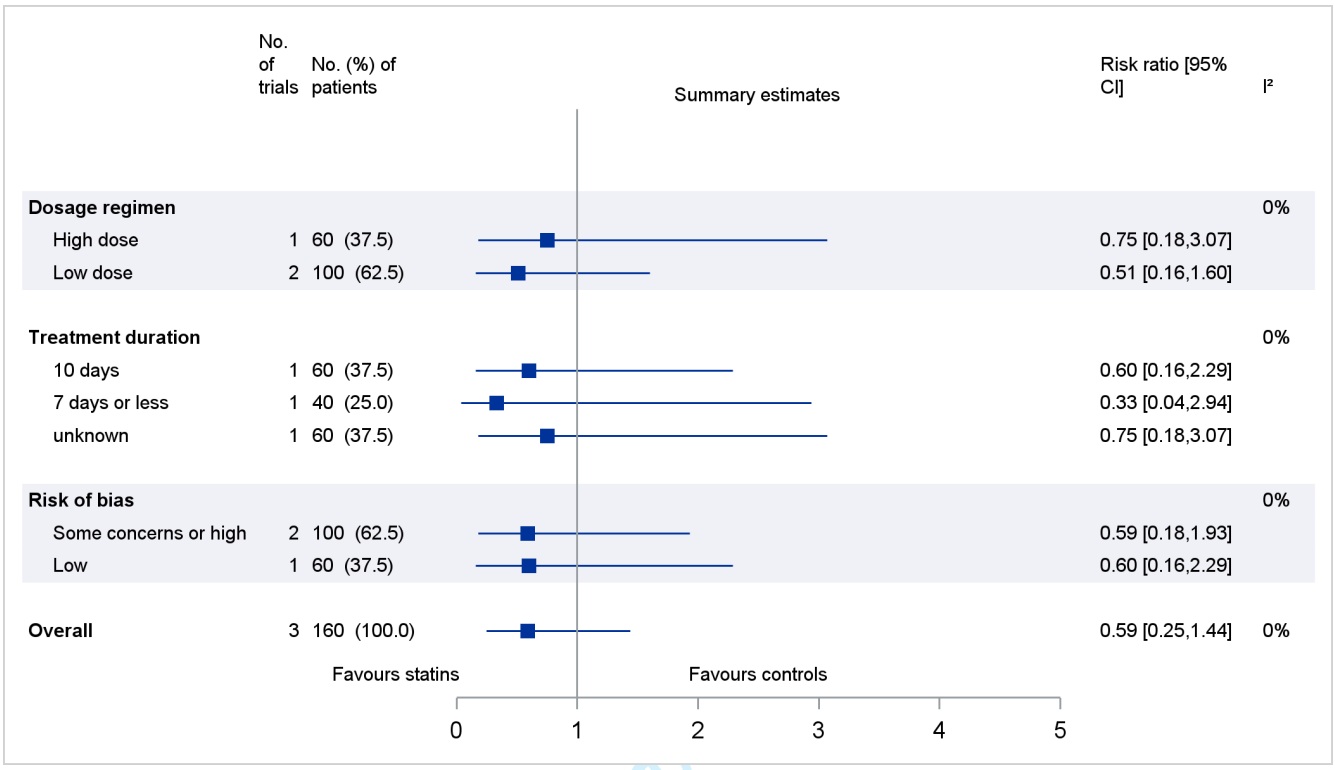

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Supplemental Material

eTable 1. Characteristics of included trials

Trials	Country, number of centers and of participants (N)	Inclusion criteria	Exclusion criteria	Initial GCS (mean ± SD)	Dosage regimen and duration	Control	Outcome measures	Timing of outcome assessment
Naghibi et al. 2016[42]	Iran Single centre N=44	Adults (older than 18 years) admitted to ICU with isolated TBI and not receiving NSAIDs, statins, or corticosteroids, had no allergy to statins, no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic, or renal disease	Sepsis during the first 72 hours of admission or did not survive the first 72 hours of admission	Intervention group: 6.6±2.5 Control group: 7.6±2.9	Simvastatin 80 mg on day 1 and 40 mg daily after Duration of therapy not mentioned	Placebo	Mortality, ICU length of stay, duration of mechanical ventilation	ICU
Farzanegan et al. 2017[43]	Iran Single centre N=64	18 to 75-year-old TBI patients with GCS 5–13 and brain contusion <30 ml on CT	Patients requiring surgery or with severe injuries to internal organs, GCS of 3 and 4, Marshall grade IV or V, severe confounding injuries to internal organs, spinal cord injury, penetrating brain injuries, renal or hepatic diseases, creatinine >2.5 mg/dl or hemodialysis, bilirubin >1.5 times normal, brain tumor, stroke,	Intervention group: 9.3±2.5 Control group: 8.4±2.7	Atorvastatin 20 mg for 10 days	Placebo	Glasgow Outcome Scale extended, contusion volume, mortality	3 months

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			infections and previous craniotomy, pregnancy or breastfeeding, INR > 1.5 or history of coagulopathy or anticoagulants, contusions in brain stem, initial SBP < 90 mm Hg without respond to fluid resuscitation, contraindications of PO medication, treatment with other investigational agents					
Soltani et al. 2020[44]	Iran Single centre N=60	18 to 50-year-old patients with isolated TBI, GCS 5–13 and brain contusion <30 ml on CT	GCS of 3 and 4, needing surgical evacuation, spinal cord injury, renal or hepatic diseases, brain tumors, stroke, previous craniotomy, INR >1.5, coagulopathy or anticoagulants before to admission, and baseline systolic BP < 90 mm Hg without responding to fluid administration	Intervention group: 5.1 Control group: 5.3	Atorvastatin 40 mg daily during ICU stay	Placebo	Mortality, duration of mechanical ventilation, ICU length of stay,	ICU
Shafiee et al.2021[45]	Iran Single centre N=98	18 to 60-year-old TBI patients with GCS <9, no allergy to statins, non-use of NSAIDs, corticosteroids, statins, no intracranial	Simultaneous injury to other organs that required surgical intervention, presence of sepsis during the first 72 hours of admission to hospital, and	Intervention group: 6.4±1.3 Control group: 6.4±1.3	Simvastatin 40 mg for 10 days	Placebo	Hospital mortality, duration of mechanical ventilation, ICU length of ICU and	30 days

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		lesion requiring neurosurgical intervention, no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic, or renal diseases	history of drug poisoning				neurosurgery ward stay	
Soltani et al. 2021[46]	Iran Single centre N=60	18 to 75-year-old patients with TBI, GCS 5–14 and brain hemorrhage 25 ml to 30 ml on CT referred to < 10 hours from injury	GCS of 3 and 4; Marshall IV or V, spinal cord injury; kidney or liver disease, creatinine > 2.5 mg/dL or patients on dialysis; brain tumor, stroke, infection, and craniotomy, pregnant and lactating women, patients with SBP < 90 mm Hg, anticoagulants within 7 days before hospitalization; contraindications to receiving oral medication	Intervention group: 8.6±3.2 Control group: 8.3±3.1	Atorvastatin 20 mg for 10 days	Placebo	Glasgow Outcome Scale, disability rating scale, mortality, ICU length of stay, hospital length of stay	3 months
Hassanin et al. 2023[38]	Egypt Single centre N=40	18 to 60-year-old acute TBI patients admitted to ICU	Patients with major organ dysfunction (renal, liver, cardiovascular), drug or alcohol abuse, allergy to statins, myopathies, pregnancy or lactation, life-threatening multiple trauma,	Intervention group: 9±0 Control group: 9.4±0.8	Simvastatin 60 mg on day 1 then 40 mg for a total of 7 days	Placebo	Glasgow Outcome Scale, mortality, ICU length of stay,	6 months

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			psychiatric disorder, prior history of neurological illness, or any trauma requiring surgery. Need for mechanical ventilation at any point during the trial					
Zarief Kamel et al. 2023[37]	Egypt Single center N=20	Adults with TBI admitted to the ICU, GSC 9-11	Pre-trial lipid lowering therapy, pre-trauma immunosuppressive, anti-inflammatory or antipsychotic medication, uncontrolled systemic disease	Intervention group: 12.5±1.72 Control group: 12.5±1.72 (GCS on ICU admission)	Atorvastatin 40 mg for 2 days	Placebo	ICU length of stay	30 days

GSC: Glasgow Coma Scale; ICU: Intensive care unit; TBI: Traumatic brain injury; CT: Computed tomography

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eTable 2. GRADE assessment for the certainty of the evidence

Certainty assessment							Nb of patients		Effect		Certainty	Importance
Nb of trials	Trial design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Statin	Control	Relative (95% CI)	Absolute (95% CI)		
Glasgow Outcome Scale												
2	RCT	Very serious[1]	Not serious	Not serious	Serious[2]	None	4/41	11/43	RR 0.42 (0.14 to 1.22)	290 fewer events per 1000 (from 430 fewer to 110 more)[3]	Very Low ⊕◯◯◯	Critical
Mortality												
3	RCT	Very serious[4]	Not serious	Not serious	Serious[5]	None	7/80	12/80	RR 0.59 (0.25 to 1.44)	123 fewer events per 1000 (from 225 fewer to 132 more)[6]	Very Low ⊕◯◯◯	Critical
ICU length of stay												
6	RCT	Very serious[7]	Serious[8]	Not serious	Serious[9]	None	149	143		MD -1.01 (-2.31 to 0.28]	Very Low ⊕◯◯◯	Important
Hospital length of stay												
1	RCT	Not serious	N/A	Serious[10]	Serious[11]	None	30	30		MD -3.70 (-4.48 to -2.92)	Very Low ⊕◯◯◯	Important

[1] Both trials had high risk of bias.
[2] Large confidence intervals caused by small number of events and overall risk ratio overlapped no effect (RR = 0.42, 95% CI :0.14, 1.22).
[3] Using a 50% risk unfavorable GOS at baseline.
[4] 1trial with a high risk of bias and 1 with an unclear risk of bias.
[5] Large confidence intervals caused by small number of events and overall risk ratio overlapped no effect (RR = 0.59, 95% CI: 0.25, 1.44).
[6] Using a 30% mortality at baseline.
[7] 4 of 6 trials included in the meta-analysis for ICU length of stay had a high risk of bias.
[8] Considerable heterogeneity among included studies (I^2 = 74%) and subgroups did not account for this heterogeneity.
[9] Large confidence intervals caused by small number of events and overall mean difference overlapped no effect (MD = -1.01, 95% CI: -2.31, 0.28).
[10] Only one trial provided data for this outcome.
[11] Large confidence intervals caused by small number of participants and overall mean difference overlapped no effect (MD = -3.7, 95% CI: -4.48, 2.92).

Legend: CI: Confidence intervals; RR: Risk ratio; MD: Mean difference

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Appendix 1. MEDLINE search strategies

((brain* [TIAB] AND injur*[TIAB]) OR (brain* [TIAB] AND traum* [TIAB]) OR (head* [TIAB] AND injur* [TIAB]) OR (head* [TIAB] AND traum*) OR (crani* [TIAB] AND injur* [TIAB]) OR (crani* AND traum* [TIAB]) OR (intracrani* and injur* [TIAB]) OR (intracrani* [TIAB] AND traum* [TIAB]) OR (intra-crani* [TIAB] AND injur* [TIAB]) OR (intra-crani* [TIAB] AND traum* [TIAB]) OR (cereb* [TIAB] AND injur* [TIAB]) OR (cereb* [TIAB] AND traum* [TIAB]) OR tbi [TIAB] OR concuss* [TIAB] OR (acute brain injuries[MeSH Terms]) OR (acute brain injury[MeSH Terms]) OR (brain injury[MeSH Terms]) OR (brain injuries[MeSH Terms]) OR (brain trauma[MeSH Terms]) OR (brain traumas[MeSH Terms]) OR (craniocerebral injury[MeSH Terms]) OR (craniocerebral injuries[MeSH Terms]) OR (craniocerebral trauma[MeSH Terms]) OR (craniocerebral traumas[MeSH Terms]) OR (diffuse axonal injury[MeSH Terms]) OR (diffuse axonal injuries[MeSH Terms]) OR (injury, diffuse axonal[MeSH Terms]) OR (injuries, diffuse axonal[MeSH Terms]) OR (closed head injury[MeSH Terms]) OR (closed head injuries[MeSH Terms]) OR (blunt head injury[MeSH Terms]) OR (blunt head injuries[MeSH Terms]) OR (coma, post head injury[MeSH Terms]) OR (intracranial hemorrhage, traumatic[MeSH Terms]) OR (hemorrhage, traumatic brain[MeSH Terms]) OR (trauma, nervous system[MeSH])) AND ((Hydroxymethylglutaryl-CoA Reductase Inhibitor*) OR (HMG CoA reductase inhibitor*) OR (hmg coenzyme a reductase inhibitor*) OR (hmg-coa reductase inhibitor*) OR (hydroxymethylglutaryl coa reductase inhibitor*) or (hydroxymethylglutaryl-coa reductase inhibitor*) OR (hmg coa statins[MeSH Terms]) OR (statins, hmg coa[MeSH Terms]) OR (statin*) OR (atorvastatin) OR (atorvaliq) OR (arkas) OR (ator) OR (atoris) OR (torvast) OR (totalip) OR (lipitor) OR (bervastatin) OR (cerivastatin) OR (baycol) OR (lipobay) OR (crilvastatin) OR (dalvastin) OR (fluvastatin) OR (lescol XL) OR (lescol) OR (lipaxan) OR (primesin) OR (fluindostatin) OR (glenvastatin) OR (lovastatin) OR (altoprev) OR (altocor) OR (mevacor) OR (monacolin) OR (mevinolin) OR (mevastatin) OR (compactin) OR (pravastatin) OR (aplactin) OR (lipostat) OR (prasterol) OR (pravachol) OR (pravaselect) OR (sanaprav) OR (selectin) OR (selektine) OR (vasticor) OR (pitavastatin) OR (alipza) OR (livalo) OR (livazo) OR (pitava) or (zypitamag) OR (rosuvatatin) OR (colcardiol) OR (colfri) OR (crativ) OR (crestor) OR (dilivas) OR (exorta) OR (ezallor) OR (koleros) OR (lipidover) OR (miastina) OR (provisacor) OR (rosastin) OR (simestat) OR (staros) OR (simvastatin) OR (alpheus) OR (flolipid) OR (krustat) OR (lipenil) OR (lipex) OR (liponorm) OR (medipo) OR (omistat) OR (rosim) OR (setorilin) OR (simbatrix) OR (sincol) OR (sinvacor) OR (sinvalip) OR (sivastin) OR (sinvat) OR (vastgen) OR (vastin) OR (xipocol) OR (zocor) OR (tenivastatin)) AND (randomized controlled trial [PT] OR controlled clinical trial [PT] OR randomized [TIAB] OR placebo [TIAB] OR drug therapy [SH] OR randomly [TIAB] OR trial [TIAB] OR groups [TIAB] NOT (animals [MH] NOT humans [MH]))

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