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

Charles Veillette ,[1] Mauricio Umana,[1] Marc-Aurèle Gagnon,[1] Olivier Costerousse,[1] Ryan Zarychanski,[2] Daniel F McAuley ,[3] Patrick Lawler,[4,5] Francois Lauzier ,[1,6] Shane W English,[7,8] Lynne Moore,[1] Chartelin Jean Isaac,[1] Alexis F Turgeon [1,9]

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For numbered affiliations see end of article.

Correspondence to
Dr Alexis F Turgeon;
alexis.turgeon@fmed.ulaval.ca

ABSTRACT

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

Objectives To evaluate the effect of statins in critically ill patients with TBI.

Design Systematic review and meta-analysis of randomised controlled trials.

Eligibility criteria Trials of adult patients with acute moderate or severe TBI.

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 GOS extended); secondary outcomes were mortality, intensive care unit (ICU) and hospital length of stay. We used inverse variance random-effects 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 Grading of Recommendations Assessment, Development and Evaluation methodology.[1]

Results Of the 2418 retrieved records, 7 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 GOS (RR 0.42; 95% CI, 0.14 to 1.22; two trials; n=84, I^2=0%; very low certainty) or mortality (RR 0.59; 95% CI, 0.25 to 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 ruled out, underscoring the need for a larger, well-designed trial.

PROSPERO registration number CRD42023421227.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our systematic review was designed to look at recommended patient-centred clinical outcomes to evaluate interventions in critically ill patients with traumatic brain injury.
⇒ Only randomised 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.

INTRODUCTION

Traumatic brain injury (TBI) affects tens of millions of individuals worldwide each year, and its incidence is increasing over time.[1 2] Despite major advances in our understanding of the disease, the optimal management of TBI patients remains uncertain, mainly focusing on preventing secondary cerebral injuries. Among the various treatment options, reducing oxidative stress has been considered one of the priorities.[3] 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.[4 5] 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.[6–12] Findings from previous systematic reviews are also conflicting,[13–20] which could be explained by differences in methods with the inclusion of non-randomised studies, TBI subpopulations or in looking at the effect of the use of statins before the TBI.[14 18 20 21] 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 randomised 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.[22] 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-Analyses Guidelines.[23] The 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 Peer Review of Electronic Search Strategies (PRESS) guidelines.[24] We identified trials using validated strategies to identify randomised controlled trials in Medline and Embase.[25 26] The strategy used for Web of Science was adapted from the Cochrane Ear, Nose and Throat Disorders group.[27] The Medline search strategy is presented in online supplemental 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

Randomised 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 moderate to severe TBI. No language restriction was applied.

Study selection and data extraction

Citations were reviewed independently by three reviewers (CV, MU and C-JI) for eligibility. The same two reviewers independently extracted data using a standardised, pretested data extraction form. Disagreements were resolved by discussion leading to consensus or by a third reviewer (AFT). 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 V.2.35 (DistillerSR; 2023, accessed March–December 2023, https://www.distillersr.com/).

Outcome measures

Our primary outcome was the Glasgow Outcome Scale (GOS) or the GOS extended (GOSe) score.[28–30] 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 corresponds to death, and a GOS of 5 or a GOSe of 8 corresponds to a full recovery. We used the common definition of an unfavourable outcome (GOS 1–3 or GOSe 1–4). Secondary outcomes were mortality, intensive care unit (ICU) and hospital length of stay. When multiple assessments over

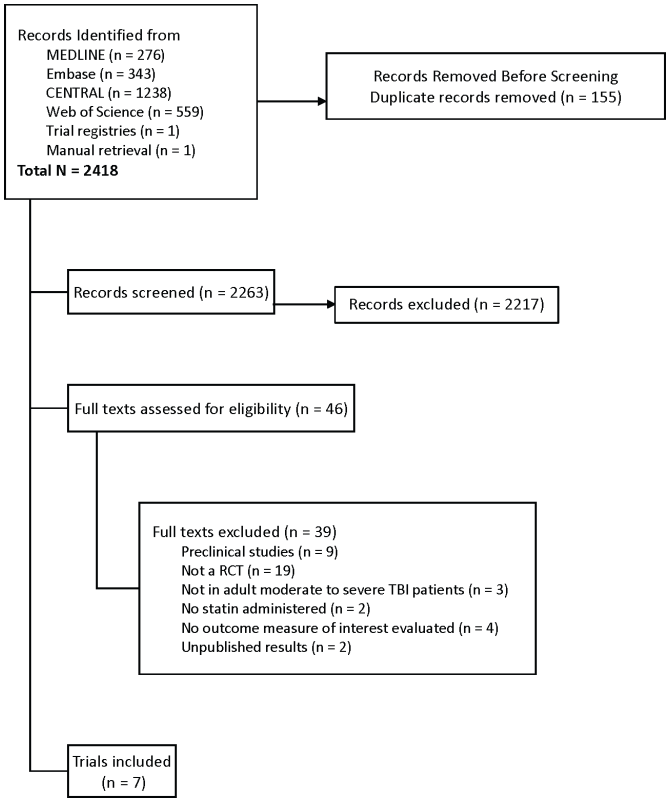

Figure 1 Flow diagram of trials. RCT, randomised controlled trial; TBI, traumatic brain injury.

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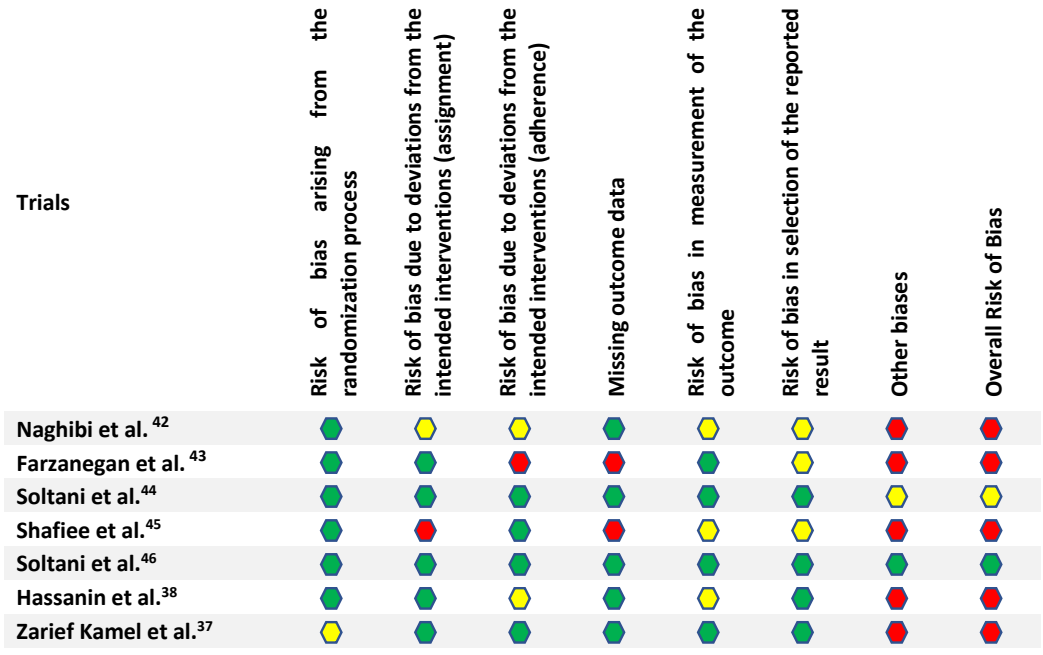

Figure 2 Risk of bias of trials.

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 (CV and C-JI) using the Cochrane Risk of Bias 2 tool.[31] Disagreements were resolved through discussions leading to consensus, or by a third reviewer if disagreement persisted (AFT). Trials were categorised as low, unclear or high risk of bias based on the worst score obtained across the six domains.

Statistical analyses

With Review Manager (V.5.4.1, The Cochrane Collaboration, 2020), we used random-effects models with the inverse variance method to calculate risk ratios (RR) for dichotomous outcomes and weighted mean differences (WMD) for continuous outcomes, with an associated 95% 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 multiple trauma), type of statins (lipophilic vs hydrophilic), dosage regimen, duration of the intervention and risk of bias of trials. We based the definition

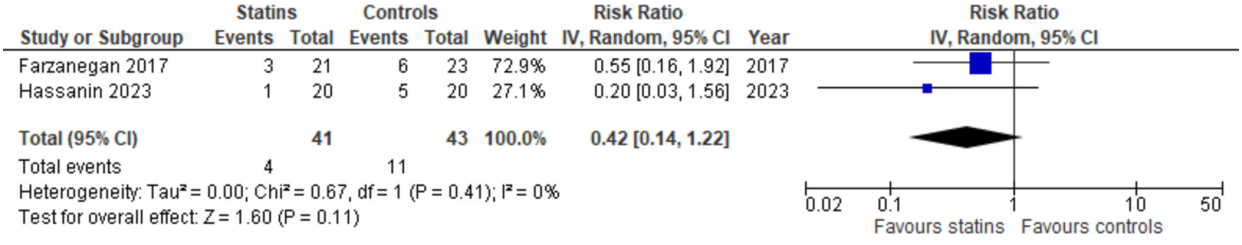

Figure 3 Effect of statins on the incidence of unfavourable neurological functional outcomes (Glasgow Outcome Scale).

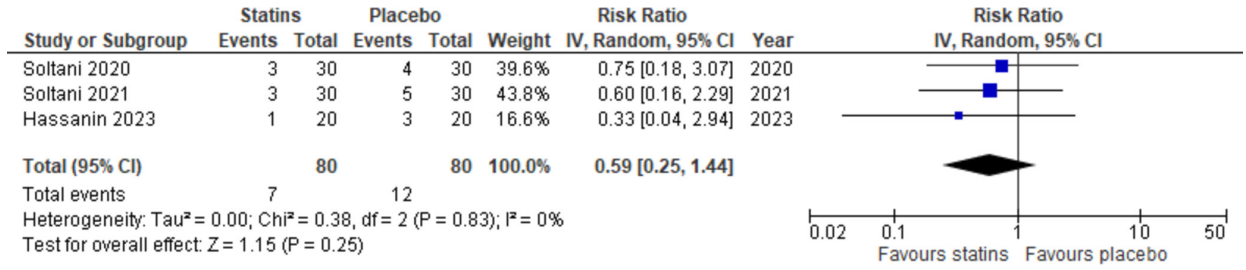

Figure 4 Effect of statins on mortality.

of dosage regimens of statins (high vs low) on the American Hearth Association/American College of Cardiology (AHA/ACC) guidelines to manage cholesterol based on the potency of each different statin.[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.[36] The final quality of evidence was classified as high, moderate, low or very low for each clinical outcome. Two reviewers (CV and C-JI) performed the classification of GRADE independently. Disagreements were resolved through discussions leading to consensus, or by a third reviewer if the disagreement persisted (AFT).

RESULTS

Our search strategy retrieved 2418 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.[37 38] 46 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 centre. Publication date ranged from 2016 to 2023 (online supplemental eTable 1). Five were conducted in Iran[42–46] and two in Egypt.[37 38] Trials enrolled 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 2 days in one trial,[37] 7 days in another trial,[38] 10 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 42–44] one at unclear risk of bias[37 44] and one 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

The GOS was reported in 3 trials,[38 43 46] representing 144 patients evaluated at 90 or 180 days. In two trials, 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 of extracting 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 GOS (RR 0.42; 95% CI,

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

Figure 5 Secondary outcomes. Random effects models with the inverse variance were used for all analyses. ICU, intensive care unit; WMD, weighted mean difference.

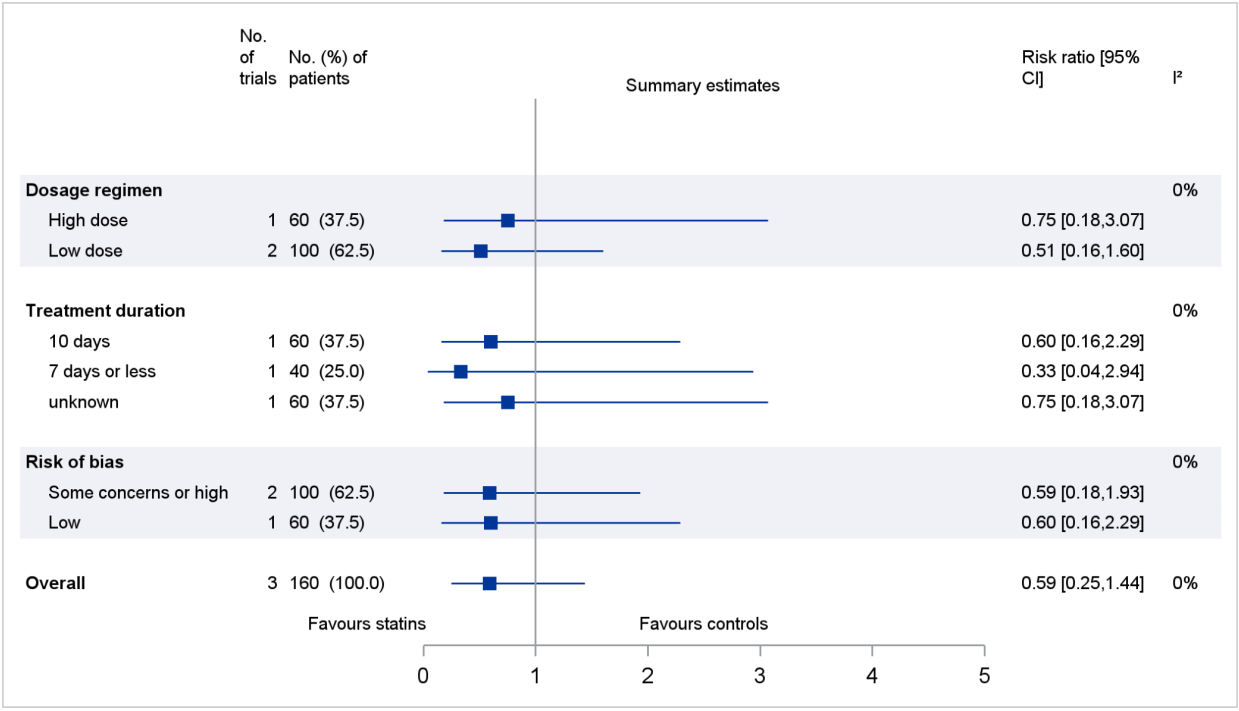

Figure 6 Subgroup analyses of mortality.

0.14 to 1.22; two trials; n=84; I^2=0%; very low certainty) (figure 3, online supplemental eTable 2). The limited number of trials precluded our ability to conduct subgroup analyses.

Mortality

Data on mortality was available in five trials[38 43 46] with a follow-up of 14–180 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 to 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 dosage regimen, duration of intervention or the risk of bias of trials (figure 6, online supplemental 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 to 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 to −2.92; one trial; n=60; very low certainty) (figure 5, online supplemental 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 patient-centred 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 beneficial in TBI patients.[13 14 18–20] Nevertheless, these reviews included non-randomised 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 unfavourable outcome with severe neurological deficits. Other reviews based their conclusions on laboratory results, which may not be clinically significant and not patient-centred outcomes. Using the GOS as our main outcome allows the evaluation of both mortality and neurological function, an outcome that is patient-centred. 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 haematoma,[21 47]

subarachnoid haemorrhage[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 haematoma resorption, decreased recurrence risk and surgical requirement in the other.[21] A recent network meta-analysis also found lower odds of recurrence of chronic subdural haematoma with the use of statins.[47] Of note, all three reviews included non-randomised studies. Two systematic reviews in patients with aneurysmal subarachnoid haemorrhage showed a decreased risk of delayed cerebral ischaemia with the use of statins. These reviews, however, showed inconsistent beneficial effects on mortality and no statistically significant difference in functional outcomes.[48 49] On the other hand, systematic reviews that investigated the effect of statins on the recurrence of ischaemic stroke in at-risk populations 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 neurological functional outcomes.

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

Our systematic review has several strengths. First, it was designed to look at patient-centred clinical outcomes to evaluate interventions in critically ill patients with TBI. Second, we considered only randomised 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 (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 with observational studies.[52–58] The application of inclusion/exclusion criteria related to clinical trial enrolment 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 neurological 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, precludes the ability to draw conclusions and recommendations in this specific patient population. A well-designed and adequately powered multicentre randomised trial evaluating the effect of statins in moderate to severe TBI patients is required.

Author affiliations
[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]Sections of Critical Care and Hematology/Medical Oncology, University of Manitoba, Winnipeg, Manitoba, Canada
[3]Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK
[4]McGill University Health Centre, Montréal, Québec, Canada
[5]University Health Network, Toronto, Ontario, Canada
[6]Department of Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada
[7]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[8]Division of Critical Care, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[9]Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Faculty of Medicine, Université Laval, Québec City, Québec, Canada

X Francois Lauzier @LauzierFrancoi1, Lynne Moore @Moore and Alexis F Turgeon @alexisturgeon_

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ORCID iDs
Charles Veillette http://orcid.org/0000-0001-8705-0059
Daniel F McAuley http://orcid.org/0000-0002-3283-1947
Francois Lauzier http://orcid.org/0000-0002-6530-5513
Alexis F Turgeon http://orcid.org/0000-0001-5675-8791

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