Supplementary Online Content

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eAppendix. Technical Appendix

This supplementary material has been provided by the authors to give readers additional information about their work.

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eAppendix. Technical Appendix

Statins and Risk of Dementia Following a Concussion

Technical Appendix

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Overview

The purpose of this appendix to summarize past literature on statin treatment to promote recovery after traumatic brain injury. The material is organized as five separate sections; namely, §1) Past Publications Before this Study, §2) Main Added Value from Current Study, §3) Integrated Implications from Combined Evidence, §4) Summary Table of Individual Studies, and §5) Collected References in Medline format. The intent is to provide a general summary of the relevant available literature.

§1) Past Publications Before This Study

Dementia is a serious and prevalent cause of disability worldwide that has lead to increasing attention to head injuries as a contributing cause and to studies testing the effect of statins on recovery after a traumatic brain injury. We searched the Medline database over multiple dates up to and including June 2018 using the search terms "head injury", 'traumatic brain injury", "concussion", 'statin", and "HMG-CoA reductase inhibitor". Searches included both English and non-English publications. This yielded 15 total publications, of which 4 were randomized studies and 11 were non-randomized studies. The details of each publication appear in the table below. The 4 randomized trials yielded conflicting results with 2 reporting a positive protective effect on neurocognitive outcomes and the other 2 reporting no significant effect. The 11 non-randomized studies also yielded conflicting results with 5 reporting a positive protective effect on neurocognitive outcomes and the other 6 reporting no significant effect. No study indicated a detrimental effect from statins following traumatic brain injury. Almost all studies focused on patients with moderate-to-severe traumatic brain injury.

§2) Main Added Value from Current Study

We evaluated a large cohort of patients diagnosed with a concussion and who were followed for an extended number of years. To our knowledge, this is the first study to report a significant potential long-term protective association between statins and the risk of dementia following a concussion. We used multiple analytic approaches to determine the long-term risk of dementia taking into account baseline patient characteristics, indications for statin therapy, adherence to statin treatment, specific statin type, and statin dose. We additionally examined the possibility of healthy-user bias by examining a separate end-point often misdiagnosed as dementia. We also examined a separate cohort of non-concussion patients to identify controls and further test possible confounding.

§3) Integrated Implications from Combined Evidence

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Our study highlights that concussions are a common adverse event in older adults and dementia is a frequent outcome years afterward. The study further suggests that a concussion should not be interpreted as a reason to stop statins. The observed neuroprotective benefit might help motivate more medication adherence for patients already prescribed a statin and who might be injured in a future concussion. The data also suggest that screening for past concussions may be warranted for patients diagnosed with dementia and that more efforts to prevent concussions are justified at all ages. The overall analytic strategies demonstrated in this study can help guide future science exploring the potential neuroprotective benefit of other medications for patients who are diagnosed with a concussion. The study also suggests that a randomized trial of statin treatment for patients in the aftermath of a concussion should be considered.

§4) Table – Summary Table of Individual Studies

Author (Year)	Study Design	Population	Sample Size	Statin	Outcomes
RANDOMIZED STUDIES (n = 4)					
Tapia-Perez (2008)[1]	RCT	Moderate traumatic brain injury (GCS 9-13), intracranial lesions on CT, age 16-50 Intervention: 20 mg rosuvastatin within 24h of injury (for 10 days) Control: placebo within 24h of injury (for 10 days)	21	Rosuvastatin	Statin improved amnesia and disorientation scores 3 months after injury (hazard ratio = 53.76, 95% CI = 1.58 to 1824.64, p = 0.027) No significant effect of statin on leukocyte, hematocrit, platelet, sodium, glucose, creatinine, TNF-α, IL-6 or IL-1β levels *Amnesia and disorientation status = assessment by blinded neuropsychologist, or positive

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					score on Galveston Orientation Amnesia Test (>75 points)
Sánchez-Aguilar (2013)[2]	RCT	Moderate or severe traumatic brain injury (GCS <13), intracranial lesions on CT, age 16-60 Intervention: 20mg rosuvastatin within 24h of injury (for 10 days) Control: placebo within 24h of injury (for 10 days)	36	Rosuvastatin	Statin reduced TNF-α levels 72 hours after injury (mean drop in TNF-α levels from baseline, rosuvastatin: 2.96 vs. placebo: 1.13, $p<0.05$) No significant effect of statin on IL-1 β, IL-6 or IL-10 levels No significant effect of statin on amnesia or disorientation scores at discharge, 3 months, or 6 months after injury (compared to placebo)
Farzanegan (2017)[3]	RCT	Moderate or severe traumatic brain injury (GCS 5-13), brain contusions <30 cm^3 volume, referred <10h of injury, age 18-75 Intervention: 20mg atorvastatin daily for 10 days, within 10h of injury Control: placebo daily	65	Atorvastatin	No significant effect of statin vs. placebo on brain contusion volume at baseline (6.06 cm^3 vs. 6.08 cm^3, $p=0.98$), Day 3 (6.24 cm^3 vs. 6.59 cm^3, $p=0.73$), or Day 7 (6.34 cm^3 vs. 6.57 cm^3, $p=0.82$) Significant improvement in functional outcomes 3 months after injury for atorvastatin vs. placebo groups: Glasgow Outcome Scale (4.57

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		for 10 days, within 10h of injury			vs. 4.09, p=0.043) Modified Rankin Scale (1.57 vs. 2.39, p=0.039) Disability Rating Scale (2.86 vs. 6.91, p=0.030)
Robertson (2017)[4]	RCT	Mild traumatic brain injury (GCS 13-15), no hospital admission, age 18-50 Intervention: 1 mg/kg atorvastatin within 24h of injury (for 7 days) Control: placebo within 24h of injury (for 7 days)	52	Atorvastatin	No significant difference in mean post-concussive symptom severity 3 months after injury (statin: 7.6, placebo: 9.2, p=0.75) No significant decrease in mean post-concussive symptoms 3 months after injury from baseline (statin: 8.1, placebo: 10.7, p = 0.35) *Post-concussive symptom severity assessed using Rivermead Post-Concussion Symptoms Questionnaire
NON-RANDOMIZED STUDIES (n = 11)					
Efron (2008)[5]	Retrospective cohort	Severe traumatic brain injury (AIS ≥ 3), lived ≥ 24 hours, age ≥ 65 Intervention: pre-	1,224	Not specified	Reduced risk of in-hospital mortality associated with pre-injury statin use (odds ratio = 0.33, 95% CI = 0.12 to 0.92, p = 0.04)

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		injury statin use Control: no pre-injury statin use			
Schneider (2011)[6]	Retrospective cohort	Severe traumatic brain injury (AIS ≥ 3), lived ≥ 24 hours, age ≥ 65 Intervention: pre-injury statin use Control: no pre-injury statin use	523	Not specified	Reduced risk of in-hospital mortality associated with statin use (relative risk = 0.24, 95% CI = 0.08 to 0.69, no p-value) Increased likelihood of good functional recovery 12 months after injury associated with statin use (relative risk = 1.13, 95% CI = 1.01 to 1.26, no p-value) No significant likelihood of good functional recovery 3 months after injury associated with statin use (relative risk = 0.83, 95% CI = 0.46 to 1.49, no p-value) *Good functional recovery = score of 6 or 7 on the Extended Glasgow Outcome Scale

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Orlando (2013)[7]	Retrospective cohort	Traumatic brain injury (GCS 3-15), hospital stay ≥ 3 days, pre-injury statin use, age ≥ 55 Intervention: statin continuation within 48h of injury Control: statin discontinuation after injury	93	Simvastatin Atorvastatin Lovastatin Pravastatin Rosuvastatin	Lower in-hospital mortality rates observed with statin continuation (continuation: 7% vs. discontinuation: 27%, p = 0.055) No significant effect on complication rate with statin continuation (continuation: 15% vs. discontinuation: 20%, p = 0.70) No significant effect on rates of hospital stay greater than 1 week with statin continuation (continuation: 23% vs. discontinuation: 18%, p > 0.99)
Wang (2014)[8]	Prospective cohort	Chronic subdural hematoma (GCS≥9) confirmed on CT or MRI, age > 16 Intervention: 20mg atorvastatin daily for 1-6 months Control: none	23	Atorvastatin	Subdural hematoma volume within 1 month of treatment was lower after statin use (baseline: 49mL vs. 1 month: 17mL, p<0.01)
Neilson	Case control	Severe traumatic brain	118	Not	No significant effect on in-

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(2016)[9]		injury (GCS ≤ 8) Intervention: pre-injury statin use Control: no pre-injury statin use		specified	hospital mortality risk (odds ratio = 1.23, 95% CI = 0.45 to 3.36, p = 0.68) No significant effect on unfavourable outcome (odds ratio = 1.19, 95% CI = 0.35 to 4.05, p = 0.78, using scores from Glasgow Outcome Scale)
Wee (2016)[10]	Prospective cohort	Traumatic brain injury (severity not specified) Intervention: pre-injury hyperlipidemia Control: no pre-injury hyperlipidemia	3,792	Not specified	Untreated hyperlipidemia increased risk of new-onset depression compared to no hyperlipidemia (hazard ratio = 1.61, 95% CI = 1.03 to 2.53, p = 0.0378) Statin-treated hyperlipidemia did not decrease risk of new-onset depression compared to untreated hyperlipidemia (hazard ratio = 0.63, 95% CI = 0.34 to 1.17, p = 0.1433)
Xu (2016)[11]	Retrospective cohort	Chronic subdural hematoma on CT or MRI , age > 16 Intervention: 20mg atorvastatin daily for 1-6 months	109	Atorvastatin	Subdural hematoma volume within 1 month of treatment was lower after statin use (baseline: 21mL vs. 1 month: 11mL, p<0.01)

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		Control: none			
Chan (2017)[12]	Retrospective cohort	Chronic subdural hematoma on CT or MRI (GCS 13 – 15), age ≥ 18, no indication for immediate neurosurgery Intervention: atorvastatin (no doses specified) Control: no atorvastatin	24	Atorvastatin	Risk of hematoma deterioration requiring neurosurgical intervention was lower in statin group compared to control group (odds ratio = 0.14, 95% CI = 0.01 to 0.96, p=0.045) Rates of hematoma resolution at 3 months were not significantly different for statin vs control groups (75% vs. 42%, p=0.09)
Khokhar (2017)[13]	Retrospective cohort	Traumatic brain injury resulting in hospital admission (severity not specified), Medicare users, age ≥ 65 Interventions: Current statin use (statins in past 2 months before injury) Recent statin use (statins in past 3-4	112,109	Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Current statin use was associated with decreased risk for in-hospital mortality (relative risk = 0.87, 95% CI = 0.82 to 0.92) Recent statin use was not associated with decreased risk for in-hospital mortality (relative risk = 0.98, 95% CI = 0.84 to 1.15) Past statin use not was associated with decreased risk for in-hospital mortality (relative

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		months, but not in 2 months immediately before injury) Past statin use (statins in past 5-6 months, but not in 1-4 months immediately before injury) Control: no statin use			risk = 0.82, 95% CI = 0.67 to 1.01)
Orlando (2017)[14]	Retrospective cohort	Traumatic brain injury (GCS 3-15), hospital stay ≥ 3 days, pre-injury statin use, age ≥ 55 Intervention: statin continuation within 48h of injury Control: statin discontinuation after injury	397	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	No significant effect on in-hospital mortality risk with statin continuation (odds ratio = 1.75, 95% CI = 0.71 to 4.31, p = 0.22) No significant effect on rates of hospital stay greater than 1 week with statin continuation (statin continuation: 29% vs. statin discontinuation: 36%, p = 0.19)
Khokhar (2018)[15]	Retrospective cohort	Traumatic brain injury resulting in hospital admission (severity not specified), Medicare users, age ≥	100,515	Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin	Post-injury statin use was associated with lower risk of mortality compared to no post-injury statin use (relative risk = 0.32, 95% CI = 0.31 to 0.33)

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		65 Intervention: statin use for at least 1 month before or after injury Control: no statin use		Simvastatin	Post-injury statin use was associated with lower risk of stroke (relative risk = 0.86, 95% CI = 0.81 to 0.91), depression (relative risk = 0.85, 95% CI = 0.79 to 0.90), and dementia (relative risk = 0.77, 95% CI = 0.73 to 0.81) compared to no post-injury statin use

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