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ORIGINAL ARTICLE

Mortality benefit of statin use in traumatic spinal cord injury: a retrospective analysis

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Study design: An observational study based on retrospective review of the medical charts and death records of 163 individuals with traumatic spinal cord injuries (SCI).
Objectives: To determine whether HMG coA Reductase Inhibitor ('statin') use in a cohort of patients with traumatic SCI reduced overall and cause-specific mortality.
Setting: An outpatient clinic designated for veterans with SCI at the Oklahoma City Veterans Administration Hospital.
Methods: Review and analysis of the medical records of 163 veterans with traumatic SCI cared for between the years 2000 and 2014. Data collected included statin use, duration of statin use and intensity of statin therapy, as well as cause-specific mortality.
Results: Seventy five participants had taken statins for an average of 5.7 ± 3.7 years, and had greater cardiovascular risk burdens than those who had not taken statins ($n = 88$). Statin use was associated with a reduced risk of death. The mortality rate for those patients on statins was 33.8–49.9 per 1000 person-years, depending on assumptions made regarding residual effects of statin use. Under most assumptions this was significantly lower than the mortality rate seen in those not on statins (47.4–66.8 deaths per 1000 person-years). Within the statin group, neither duration nor average intensity of statin therapy affected mortality.
Conclusion: Statin use among a cohort of veterans with traumatic SCI reduced all-cause mortality. This retrospective study ought to spur further investigations into the potential benefits of statin use among people with chronic SCI, and begin a discussion as to whether individuals with injuries should routinely be offered statin therapy.
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INTRODUCTION

A growing literature suggests that chronic spinal cord injury (SCI) is accompanied by severe atherosclerotic arterial disease. Bauman *et al.*[1] performed thallium stress tests on 20 middle-aged men with SCI, 13 of whom had positive results and 8 of whom had multi-vessel 'moderate to severe' disease. Lee *et al.*[2] conducted cardiac stress tests on 47 asymptomatic participants with SCI, describing injury-dependent ischemic changes in 50–85% of them. Orakzai *et al.*[3] calculated coronary artery calcium scores on well-matched injured and non-injured participants, finding significantly higher scores in those with SCI. Bell *et al.*[4] performed ankle brachial indexes in participants with and without SCI, describing significantly reduced blood flow among participants with injuries.

Concern over atherosclerotic disease in chronic SCI is warranted, as individuals with SCI have significantly shorter life expectancies than those without,[5,6] and cardiovascular disease is their leading cause of mortality.[7,8] In a single study of 54 people with chronic tetraplegia randomized to extended release Niacin monotherapy ($n = 31$) or matched placebo ($n = 23$) for 48 weeks, Nash *et al.* found that treatment with Niacin led to significant improvements in lipid profiles.[9] However, no trials to date have sought means to reduce cardiovascular morbidity and mortality in SCI, nor to begin to close the 'longevity gap' between people with and without injuries. Two recent studies have confirmed the high prevalence of hypertension, diabetes mellitus and dyslipidemia among patients with traumatic SCI, and the need to screen for and treat them accordingly.[10,11]

We recently showed that cardiovascular disease had caused 25% of deaths among our clinic patients with SCI.[12] We hypothesized that a retrospective analysis of their medical and death records would reveal that HMG CoA Reductase Inhibitor ('statin') use during this study period had reduced both overall and cardiovascular-specific mortality.

MATERIALS AND METHODS

In this observational study, we retrospectively reviewed the electronic charts of all 165 veterans with traumatic SCI who had been registered in the SCI program at the Oklahoma City Veterans Administration Medical Center since 1 January 2000 and followed in its outpatient clinic. Electronic data were retrieved by one of the authors (MHR), and were cross checked for accuracy with the list maintained by the SCI program. Two patients were excluded because of incomplete data, but otherwise no exclusion criteria were applied. Thus, 163 patients were included in this analysis.

During physician visits, participants had been routinely assessed for current medical conditions such as urinary tract infection, pneumonia, myocardial infarction, congestive heart failure and arrhythmias, and strategies for managing neurogenic bowel and bladder, skin integrity and modifiable vascular risk factors were addressed. Some participants were on statin therapy at the time of

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their initial evaluations, some were found to be hyperlipidemic and started on statins, and others were never prescribed them.

Participants' age at injury, duration of injury, sex, ethnicity, level and severity of injury (ASIA Impairment Scale (AIS) grade: A–E), and fasting lipid profiles were recorded at their initial evaluations, and data on their modifiable vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, body mass index and current smoking status), current cardiovascular status (coronary artery disease and congestive heart failure) and SCI-related complications (depression, pressure ulcer with or without osteomyelitis, and neurogenic bowel or bladder) were gathered at each follow-up visit. Participants' records were reviewed to determine whether or not they had been treated at any time during the study period with any available statin, and survival was recorded up until 30 September 2014, with cause of death obtained from each subject's death certificate. The local Institutional Review Board for Human Subjects Research and the local Veterans Affairs Research and Development Committees' approval were obtained for the study.

For participants who had been treated with statins, data were collected on duration of statin therapy, which agent(s) he/she had been prescribed, and 'intensity' of treatment. Intensity was estimated using American College of Cardiology/American Heart Association[13] statin classification, with 'low-intensity' statins assigned the number 1, 'moderate-intensity' statins assigned the number 2, and 'high-intensity' statins assigned the number 3. Each participant's total statin exposure was then summarized as a time weighted average:

$$\text{INTavg} = \frac{\sum (\text{yrs on statin j}) \times (\text{intensity statin j})}{\text{Total yrs on statin therapy}}$$

where the sum is over the different statins that the participant was exposed to. For example, a participant who was on a high-intensity statin for 2 years, then a low-intensity statin for 4 years would have INTavg = $(2\times3+4\times1)/(2+4) = 10/6 = 1.67$. For our analysis, INTavg was rounded upward or downward to the nearest whole number.

Statistics

Group descriptive statistics were expressed as mean ± s.d. and grouped frequencies. Differences in demographics, cardiovascular risk factors and lipid levels between groups were assessed using generalized linear models. Mortality rates were calculated as deaths per 1000 person-years at risk. Kaplan–Meier survival curves were estimated for the no-statin group and statin groups and compared using a log-rank test. Data analyses were conducted using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp.), and results corresponding to *P*-values $<5\%$ are described as significant for the purposes of discussion.

RESULTS

Baseline characteristics for the participants ($n = 163$) are broken down by statin use and shown in Table 1. Not surprisingly for a VA clinic, men comprised 98% of participants, 81% were non-Hispanic Whites, average age at time of SCI was 39 ± 16 years, and average duration of injury before first clinic visit was 19 ± 16 years. Just over half of the participants (55%) had cervical level injuries, half (50%) were classified as 'motor complete' (AIS A or B) and 48% had been injured as the result of a motor vehicle accident.

Cardiovascular risk factors were prevalent among participants: 53% had hypertension, 24% had diabetes mellitus, 48% had hyperlipidemia, 51% were overweight with a body mass index over 25 kg m^{-2} and 38% were current smokers. Prevalence of each risk factor except for smoking was higher in the statin than in the non-statin group, those taking statins had a greater number of cardiac risk factors, and a larger percentage of statin-treated participants had myocardial infarctions. The initial low-density lipoprotein levels for the two groups were not significantly different, and was 113 ± 48 in the 56 veterans who began taking statins during the study period (19 were already on them).

Participants treated with statins had been offered variable regimens over the 15-year follow-up period. Average duration of statin therapy was 5.7 ± 3.7 years, and the vast majority (67%) of treated participants took moderate-intensity statins. In the statin-treated group, 28 participants died during follow-up, 16 while still taking statins ('on statins'), the rest having discontinued therapy 2–10 years before their deaths ('post-statins').

There was a significant reduction in mortality among participants taking statins (Table 2). Despite carrying heavier burdens of cardiovascular risk factors, 37% of those who had been on statin therapy at some point during the 15 years vs 58% of those who had never been on therapy died. Although not reaching statistical significance, a lower percentage of participants on statins than not on statins died from cardiovascular disease and pulmonary complications. Those who had never taken statins averaged 1.6 years less follow-up than those who had, however, 42% of patients in both groups were followed for a full 15 years. Kaplan–Meier survival curves are shown in Figure 1 with a significant difference between the groups ($P = 0.0052$).

The 88 patients who had never taken statins accumulated 748 person-years of risk during which 50 of them died. This yields an estimated mortality rate of 66.8 deaths per 1000 person-years. If the 310 person-years (with no deaths) accumulated by the statin group before starting statin therapy is included, this mortality rate drops to (50+0)/(748+310) = 47.3 per 1000 person-years. The 75 patients in the statin group accumulated 473 person-years of on treatment risk during which 16 of them died. This yields an estimated mortality rate of 33.8 per 1000 person-years, significantly lower than both 66.8 per 1000 person-years ($P<0.0001$) and 47.3 per 1000 person-years ($P<0.0001$) and with rate ratios of 33.8/66.8 = 0.51 and 33.8/47.3 = 0.71, respectively.

Of the 75 individuals who started statin therapy, 20 stopped due to adverse medication effects (primarily gastro-intestinal effects or muscle pain), accumulating 88 person-years of post-statin risk. Twelve of these 20 died during follow-up, resulting in an estimated mortality rate of 136.4 per 1000 person-years. The 12 deceased patients averaged 4.4 ± 2.3 years post-statin therapy (range 2–10 years), whereas the 8 survivors averaged 4.4 ± 2.6 years post-statin therapy (range 2–9 years). Assuming that statin use played no role in the deaths of the 'post-statin' participants, the death rate ratio would seem to favor statin therapy. The mortality rate for the 'on statin' cohort was 33.8 per 1000 person-years, whereas that for the no-statin group (including those who discontinued treatment) was (50+0+12)/(748+310 +88) = 54.1 per 1000 ($P<0.001$). This yields a rate ratio of 0.62. However, the assumption that statin use or cessation contributed to these deaths would demand an 'intention-to-treat' analysis, comparing mortality rates of those not on statins (47.3 per 1000 person-years) to those on statins irrespective of whether they had discontinued therapy ((16 + 12)/(473 + 88) = 49.9 per 1000 person-years). In this case, the rate ratio would be 1.05.

Within the statin group, neither duration nor intensity of statin therapy influenced mortality or cause of death. The 47 statin group members who survived the study period averaged 6.8 ± 4.1 years of therapy, whereas the 28 who died had taken statins for an average of 6.7 ± 3.4 years. Those who died post-statin therapy had averaged 3.8 ± 2.5 years of treatment, significantly less than either of the previous groups ($P = 0.0026$ and 0.014, respectively).

Among statin users, there was no difference in medication intensity between those who survived and those who died (INTavg: 2.2 ± 0.4 vs 2.1 ± 0.6, $P = 0.32$). Forty six percent of the 50 patients who averaged 'moderate' intensity treatment died, with just over half doing so while

Table 1 Demographic data and cardiovascular risk factors/lipid levels for the total cohort, as well as for the statin and non-statin groups (mean ± s.d. or *n* (%))

Characteristic	*Total population*	*On statins*	*Not on statins*	P-*value statins* vs *no statins*
N	163	75	88	
Age at occurrence of SCI (years)	39 ± 16	41 ± 16	37 ± 15	0.12[a]
Age at entry to study (years)	55 ± 14	55 ± 12	55 ± 16	0.99[a]
Time from SCI to entry (years)	16 ± 15	14 ± 14	18 ± 16	0.14[a]
Gender (M:F)	159:4	73:2	86:2	0.87[b]
Ethnicity (White/Black/American Indian/Hispanic)	132/22/5/4	64/8/2/1	68/14/3/3	0.59[b]
Spinal injury level				0.91[b]
Cervical	90 (55)	40 (53)	50 (56)	
Thoracic	50 (31)	24 (32)	26 (30)	
Lumbosacral	23 (14)	11 (15)	12 (14)	
Spinal injury completeness – ASIA				0.047[b]
A	56 (34)	26 (35)	30 (34)	
B	25 (15)	5 (7)	20 (23)	
C	31 (19)	18 (24)	13 (15)	
D	37 (23)	20 (27)	17 (19)	
E	14 (9)	6 (8)	8 (9)	
Motor complete (AB)	81 (50)	31 (41)	50 (57)	0.049[b]
Motor incomplete (CDE)	82 (50)	44 (59)	38 (43)	
Etiology of SCI				0.11[b]
Motor vehicle accident	79 (48)	31 (41)	48 (54)	
Gunshot	18 (11)	7 (10)	11 (13)	
Fall	45 (28)	26 (35)	19 (22)	
Diving	5 (3)	1 (1)	4 (4)	
Other	16 (10)	10 (13)	6 (7)	
Risk factors				
Hypertension	76 (53)	50 (69)	26 (37)	0.0001[b]
Diabetes mellitus	37 (24)	27 (36)	10 (13)	0.0009[b]
Hyperlipidemia	68 (48)	57 (78)	11 (16)	<0.0001[b]
Body mass index	26.8 ± 7.6	28.8 ± 7.0	25.1 ± 7.8	0.0030[a]
% With BMI >25	51	68	37	0.0002[b]
Current smoker	62 (38)	28 (38)	34 (42)	0.60[b]
Total cholesterol	162 ± 40	164 ± 49	160 ± 30	0.56[a]
Triglycerides[c]	142 ± 115	146 ± 69	139 ± 143	0.092[a]
LDL cholesterol	105 ± 37	108 ± 44	101 ± 29	0.28[a]
HDL cholesterol	40 ± 28	42 ± 38	39 ± 13	0.62[a]
Co-morbidities				
Myocardial infarction	26 (17)	17 (24)	9 (11)	0.028[b]
Congestive heart failure	8 (5)	5 (7)	3 (4)	0.39[b]
Depression	72 (46)	42 (56)	30 (36)	0.012[b]
Pressure ulcers	49 (31)	16 (23)	33 (38)	0.038[b]
Osteomyelitis	18 (15)	5 (10)	13 (10)	0.18[b]
Neurogenic bowel	81 (55)	41 (61)	40 (49)	0.15[b]
Neurogenic bladder	130 (84)	63 (84)	77 (85)	0.89[b]

Abbreviations: BMI, body mass index; HD, high-density lipoprotein; LDL, low-density lipoprotein; SCI, spinal cord injury.
[a]Student's *t*-test.
[b]χ^2 Test.
[c]Measure was log-transformed for analysis; mean ± s.d. provided are for untransformed values.

on statin therapy. Four of the 16 participants who averaged 'high' intensity therapy died, 3 while still being treated. Only one of the nine patients who had been on 'low' intensity therapy died, and he had stopped therapy 4 years prior. A chi-squared analysis comparing the distribution of high, moderate and low-intensity therapy between those who died and those who survived while taking statins suggested that neither higher nor lower intensity therapy improved survival ($P = 0.071$).

Cause of death (Table 2) was not significantly different between those treated or not treated with statins, although the decrease in respiratory related deaths suggests need for further investigation. Likewise, although the sample sizes were small, there was no

Table 2 Overall mortality and cause of death among statin and non-statin groups (mean ± s.d. or *n* (%))

Characteristic	*Total Population*	*On Statins*	*Not on Statins*	*P-value statins vs no statins*
N	163	75	88	
Follow-up (years)	10.8 ± 4.7	11.6 ± 4.0	10.0 ± 5.2	0.033[a]
Deaths (%)	79 (49%)	28 (37%)	51 (58%)	0.0087[b]
Age at death (years)	66 ± 12	66 ± 10	66 ± 13	0.86[a]
Cause of death (% of deaths)				0.39[b]
Respiratory	22 (28%)	6 (21%)	16 (31%)	
Cardio	12 (15%)	4 (14%)	8 (16%)	
Cancer	12 (15%)	3 (11%)	9 (17%)	
Sepsis	7 (9%)	3 (11%)	4 (8%)	
UTI	7 (9%)	1 (4%)	6 (12%)	
Stroke	4 (5%)	2 (7%)	2 (4%)	
Other	3 (4%)	2 (7%)	1 (2%)	
Unknown	12 (15%)	7 (25%)	5 (10%)	

[a]Student's *t*-test.
[b]χ^2-test.

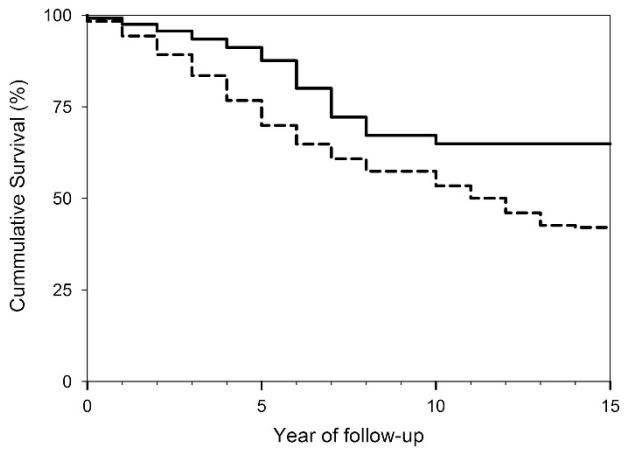

Figure 1 Estimated overall survival for patients with traumatic SCI (tSCI) stratified by statin use. Those on statins are shown by a solid line; those not on statins are shown by a dashed line. Survival for those on statins begins from the year they started statins or the year they entered the study (whichever came later); survival for those not on statins begins from the year they entered the study.

significant difference in distribution of causes of death between those who died while on statins and those who died post-statin therapy.

DISCUSSION

Statins have been proven effective for secondary prevention in heart disease. Their use in the Scandinavian Simvastatin Survival Study ('4S') was associated with a 42% reduction in cardiac deaths,[14] CARE and LIPID trial participants on statins suffered fewer fatal and non-fatal myocardial infarctions,[15,16] and statin-treated participants in the Heart Protection Study had a 20% decrease in major cardiovascular events.[17]

Despite compelling evidence that chronic SCI is attended by severe atherosclerotic disease, that cardiovascular disease is the leading cause of mortality in SCI, and that people with SCI have shortened life expectancies, statins have yet to be rigorously studied in individuals with chronic injuries. This is the first paper to suggest that statin therapy may decrease mortality for people living with chronic SCI, and may hopefully spark interest in prospective treatment trials to address this important issue.

Our most significant finding is that statin therapy in a cohort of chronically injured veterans was associated with a decrease in mortality. Even though participants on statins had more cardiovascular risk factors and higher rates of heart disease than those not taking statins, their mortality rate was between 33.8 and 49.9 deaths per 1000 person-years over 15 years of follow-up, depending on whether strictly on statin therapy or intention-to-treat is considered. During that same period, the mortality rate for non-statin users was between 47.3 and 66.8 deaths per 1000 person-years. Although these findings are not definitive, they suggest that under most analytical assumptions statin use leads to large and significant reductions in mortality among people with traumatic SCI. These data ought to prompt further study of how statin therapy may benefit individuals with SCI, and if confirmed in future trials, would represent a notable development in the clinical care of people living with injuries.

A second important observation is that while statin-driven reduction in overall mortality was partly explained by cardiovascular benefit, statin treatment was also associated with a reduced, though not statistically significant, risk of death from respiratory complications. Although still controversial,[18] several studies have indicated that statin use lowers risk of contracting and dying from community-acquired pneumonia,[19–21] and proposed protective mechanisms include maintenance of vascular and endothelial integrity, modulation of neutrophil function, and a reduction in systemic and, ultimately, maladaptive coagulation.[22,23] As respiratory complications are the second leading cause of death in SCI,[7] a statin-associated reduction in pulmonary fatalities, if validated in future studies, would be a welcomed and crucial finding.

Third, we were surprised that within the statin group, neither intensity nor duration of therapy influenced cause of death or overall mortality. In the 'Prove-It' trial, participants with acute coronary syndromes treated with Atorvastatin 80 mg per day had significant reductions in mortality and major cardiovascular events when compared with those treated with Pravastatin 40 mg per day.[24] In the 'TNT' trial, participants with stable coronary artery disease on a high-intensity statin had fewer cardiovascular events than those taking a moderate-intensity agent.[25] It is likely that our subject pool was not powered to detect intensity-dependent changes in mortality and that too few of our participants were taking high-intensity regimens for proof of benefit to emerge. It may also simply be that statin-treated participants benefitted from the agents' 'pleiotropic' effects, which are known to include improving endothelial dysfunction, reducing platelet reactivity, increasing numbers of circulation endothelial progenitor cells, and stabilizing atherosclerotic plaques.[26,27] Future studies with greater numbers of participants may help optimize statin-based treatments for people living with injuries, and help to determine whether they, like others with 'coronary artery disease equivalent' conditions, ought to be offered higher-intensity agents.

Our analysis was limited in several critical ways. First, our cohort was relatively small, and female and non-White participants were under-represented. Future studies enrolling more participants, and specifically recruiting these under-represented groups, may yield clearer and more specific results, and be applicable to greater numbers of people living with spinal cord injuries. Second, retrospective reviews are inherently limited and biased. Blinded therapeutic statin trials in this vulnerable population are certainly needed, and will likely allow us to collect more robust and definitive data. Third, duration and intensity of statin therapy varied widely among our participants, and

as our numbers were small, this study cannot offer clear answers as to the true benefits of various treatment regiments. Forth, a consequence of the small sample size was that Cox-proportional hazards models used to estimate the effect of statin use on mortality with simultaneous adjustment for other risk factors failed to converge. Further epidemiological research based on a larger patient population or controlled trials are needed to allow more precise conclusions to be drawn. Finally, the prevalence of statin use increased 10-fold in our study from 4% in 2000 to a roughly constant prevalence of 40% from 2007–2014, and it is impossible to determine how, exactly, that shift shaped our results. Despite these weaknesses, however, this report serves as a catalyst for more definitive and larger prospective studies, and offers the hope that utilization of widely available statins may significantly benefit individuals with chronic SCI.

CONCLUSION

Given that individuals with chronic SCI carry significant atherosclerotic burdens, have shortened life spans, and most frequently die from cardiovascular disease, this study provides the first suggestion that statin use may significantly improve mortality among people living with SCI. Depending on which assumptions are made, the mortality rate for statin users was in the range 33.8–49.9 per 1,000, whereas the rate for non-users was 47.3–66.8. Hence this preliminary study suggests an unadjusted relative risk in the range 0.51–1.05.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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