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In-Hospital Mortality Following Traumatic Brain Injury Among Older Medicare Beneficiaries, Comparing Statin Users With Nonusers

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Abstract

Background: Traumatic brain injury (TBI) is a significant public health concern for older adults. Small-scale human studies have suggested pre-TBI statin use is associated with decreased in-hospital mortality following TBI, highlighting the need for large-scale translational research. **Objective:** To investigate the relationship between pre-TBI statin use and in-hospital mortality following TBI. **Methods:** A retrospective study of Medicare beneficiaries 65 and older hospitalized with a TBI during 2006 to 2010 was conducted to assess the impact of pre-TBI statin use on in-hospital mortality following TBI. Exposure of interest included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Beneficiaries were classified as current, recent, past, and nonusers of statins prior to TBI. The outcome of interest was in-hospital mortality. Logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) comparing current, recent, and prior statin use to nonuse. **Results:** Most statin users were classified as current users (90%). Current atorvastatin (OR = 0.88; 95% = CI 0.82, 0.96), simvastatin (OR = 0.84; 95% CI = 0.79, 0.91), and rosuvastatin (OR = 0.79; 95% CI = 0.67, 0.94) use were associated with a significant decrease in the risk of in-hospital mortality following TBI. **Conclusions:** In addition to being the most used statins, current use of atorvastatin, rosuvastatin, and simvastatin was associated with a significant decrease in in-hospital mortality following TBI among older adults. Future research must include clinical trials to help exclude the possibility of a healthy user effect in order to better understand the impact of statin use on in-hospital mortality following TBI.

Keywords
trauma medicine, cardiovascular drugs, trauma, geriatrics, pharmacoepidemiology

Introduction

In 2010, traumatic brain injury (TBI) caused more than 50 000 deaths in the United States.[1] While a concern for all Americans, TBI disproportionately affects older adults due to their higher risk of falls.[1-4] The rate of TBI hospitalization in the United States is more than 3 times greater in adults over 65, compared with adults aged 45 to 64.[4] Among older adults 65 and older, TBI mortality rates from 2009 to 2010 was 45.2 per 100 000 people.[4] Furthermore, mortality rates for TBI in older adults also increase with age.[5]

TBI is characterized by damage to brain tissue, which can lead to inflammation and abnormal cerebral blood flow (CBF).[6] The inflammation and abnormal CBF from the primary injury, the initial insult, can lead to mortality.[7,8] Currently, several pharmacotherapies have been suggested to reduce mortality following TBI.[9,10] The variety of treatment options for TBI led to the creation of the Operation Brain Trauma Therapy (OBTT), a research consortium created to screen and advance novel biomarkers and therapies for TBI, from animal studies to human clinical trials.[11] The OBTT has highlighted several therapies that can potentially be used for TBI patients, including statins.[11]

In addition to their primary utility in reducing serum cholesterol, statins decrease inflammation and increase

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CBF.[15] Statins accomplish this by limiting the production of inflammatory cytokines and promoting blood-brain barrier integrity.[10,12,13] These properties may help preinjury statin use to decrease in-hospital mortality, and a few small-scale studies have suggested this relationship.[14,15]

Given the potential of statins to reduce mortality indicated in prior small-scale human research, the objective of this study was to assess the relationship between pre-TBI statin users and nonusers who suffer a TBI and subsequent in-hospital mortality in a large-scale population of older Medicare beneficiaries.

Methods

Study Sample

Centers of Medicare & Medicaid Services (CMS) data were used to investigate preinjury statin utilization and in-hospital mortality following hospital admission for TBI. These data contain 100% of Medicare beneficiaries who were hospitalized with a TBI during 2006 to 2010 and who had continuous Medicare Parts A, B, and D. TBI was identified through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, 950.1-950.3, and 959.01. These codes have been used to define TBI in prior research utilizing Medicare claims data.[16-18] Multiple TBI admissions occurring within 14 days were counted as a single TBI, with the admission date for the first TBI being the index date. This approach has been previously used to account for the likelihood of multiple TBI claims being made for the care of a single TBI.[16-18]

Beneficiaries were required to be at least 65 at the time of their first TBI and have at least 6 months of continuous Medicare Parts A, B, and D coverage prior to TBI. Medicare Parts A, B, and D include inpatient, outpatient, and prescription drug claims, respectively. Beneficiaries with Medicare Part C are part of managed care programs and their medical claims are not available; therefore, these beneficiaries were excluded.

Exposure

The exposure of interest was statins, which comprised atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Combination drugs that contained a statin were classified as that individual statin; for instance, beneficiaries using ezetimibe/simvastatin were classified as using simvastatin. Statin use prior to TBI was determined per 30-day period relative to TBI. If beneficiaries had a fill for a statin or a proportion of days covered (PDC) during a 30-day period, the beneficiary was flagged as using statins in that period.[17] PDC was calculated by dividing the number of days a drug was available in a period by the number of days in a period (30 days).[19] Each beneficiary had six periods (hereafter referred to as months) of statin use or nonuse information prior to TBI.

Statin users (by class and by individual statins) and nonusers were classified into 4 mutually exclusive categories: current use (use in any of the 2 months immediately prior to TBI); recent use (use in 3 or 4 months and no use in 1 or 2 months prior to TBI); prior use (use in 5 or 6 months and no use in 1 to 4 months prior to TBI); and no use in any month prior to TBI.

Outcome

The outcome of interest was in-hospital mortality, which was observed through inpatient Medicare claims data. In-hospital mortality was flagged if beneficiaries were discharged dead following index TBI. Beneficiaries were censored following hospitalization discharge.

Covariates

Covariates included demographic characteristics (age, race, and sex) and chronic conditions. Overall health was determined by including a comorbidity count excluding cardiovascular disease (CVD; hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heart disease, and diabetes) and Alzheimer's disease and related dementias (ADRD). CVD and ADRD were added separately because of their association with statin use and mortality.[20] A skilled nursing facility (SNF) stay in the month prior to TBI was included to determine overall health as an SNF stay may be indicative of poor health.[17,18]

Medication use that may affect survival following TBI (antiplatelets, anticoagulants, beta-blockers, and other statins used) also were included as covariates.[17] TBI severity was calculated by the ICD-9-based independent survival risk ratios (SRRi). SRRi are calculated by dividing the number of survivors in each injury (ICD-9-CM code) by the total number of patients with the same injury.[21] The SRRi per injury per beneficiary are multiplied together to obtain an injury severity score.[21] Additionally, length of hospital stay also was included as a TBI severity proxy measure.

Lastly, Area Health Resources Files (AHRF) data, linked to CMS data through Social Security Administration's county codes, was used to include demographic and health care–related geographical characteristics. Therefore, county-level demographic covariates (median income and geographical region) and provider and hospital characteristics per 100 000 people (total physicians, hospitals, hospitals with trauma services, hospitals with neurological services, and beds) were included.

Data Analysis

Bivariate analysis was conducted to compare the baseline descriptive and sociodemographic characteristics of statin users and nonusers. Chi-square and *t* tests were used to assess significant differences for categorical and continuous variables, respectively. A Wilcoxon rank sum test was used to assess differences in medians between statin users and nonusers. Logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for mortality, comparing current, recent, and prior statin use to nonuse. Furthermore, additional analysis was conducted comparing statin use per each individual month prior to TBI with nonuse, rather than comparing the categorical use variables of current use, recent use, and prior use with nonuse.

To better understand the impact of statin use and in-hospital mortality, the relationship between different statin doses and in-hospital mortality was examined among statin users for the statins that indicated a significant protective effect against in-hospital mortality. This analysis was conducted by comparing statin doses at the monthly level among statin users prior to TBI for only the months that statin use indicated a protective effect against in-hospital mortality. Statin doses for comparison were selected by examining the distribution of statin doses.

Similarly, secondary analysis was conducted examining 30- and 60-day mortality following TBI, investigating the statins that indicated a protective effect on in-hospital mortality, comparing current statin users to nonusers. This was done to understand the lasting impact of pre-TBI statin use in the one or two months immediately prior to TBI.

Last, sensitivity analysis was conducted to assess robustness of results after excluding beneficiaries who died within 24 hours of TBI hospitalization. This approach has been used in prior studies in order to exclude the most severe TBIs.[14,15]

All analyses were performed with SAS version 9.2 (Cary, NC). This study was approved by the University of Maryland Baltimore's International Review Board.

Results

A total of 116 193 Medicare beneficiaries had a TBI during 2006 to 2010; of these individuals, 112 716 were at least 65 years old at the time of their TBI and had continuous coverage of Medicare Parts A, B, and D 6 months prior to their index TBI. An additional 607 beneficiaries were excluded due to missing prescription drug information because these beneficiaries had a hospital or SNF stays throughout the study period and prescription drug claims are not available during facility stays. Thus, the final sample included 112 109 beneficiaries.

A total of 45 752 (41%) beneficiaries used statins at some point prior to TBI. Overall, the majority of the sample was white (87%) and female (64%). Statin users were younger (80 years compared to 82 years, $P < .0001$) and had slightly higher median income ($50 660 compared to $49 518, $P < .0001$). While 97% of statin users had hyperlipidemia, the majority (60%) of nonusers also had hyperlipidemia. There were no significant differences in the TBI severity measures (Table 1).

Most statin users were classified as current users 41 174 (90%), while 2852 (8%) were classified as recent users and 930 (2%) were classified as past users. The most commonly used statins were simvastatin and atorvastatin (Appendix Table 1). A total of 9810 (9%) of beneficiaries were discharged dead following TBI hospitalization.

In adjusted analysis, current use of any statins was associated with decreased in-hospital mortality (OR = 0.87; 95% CI = 0.82, 0.92). When assessing individual statins, current use of atorvastatin (OR = 0.88; 95% CI = 0.82, 0.96), rosuvastatin (OR = 0.79; 95% CI = 0.67, 0.94), and simvastatin (OR = 0.84; 95% CI = 0.79, 0.91) were associated with a significant decrease in the risk of in-hospital mortality following TBI. Recent use and past use of any statin was not associated with a decreased risk of in-hospital mortality (Table 2).

Analysis assessing statin use per month prior to TBI indicated that any statin use, atorvastatin use, rosuvastatin use, and simvastatin use in the month immediately prior to TBI was associated with a decreased risk of in-hospital mortality when compared with nonuse (Table 3). The relationship between statin dose in the 2 months prior to TBI and in-hospital mortality was assessed for these 3 statins. Statin doses were categorized by examining the most prominent doses among beneficiaries (Appendix Table 2). This analysis, conducted only among statin users, found no relationship between atorvastatin and rosuvastatin dose and mortality. However, higher doses of simvastatin were significantly associated with a decrease in in-hospital mortality (Appendix Table 3).

Secondary analysis examining 30- and 60-day mortality comparing current use of atorvastatin, rosuvastatin, and simvastatin indicated that all three statins significantly reduced 30-day mortality and rosuvastatin and simvastatin significantly reduced 60-day mortality (Table 4).

Sensitivity analysis restricted to beneficiaries who did not die with 24 hours of hospitalization showed similar results as the primary analysis (Appendix Tables 4-6).

Discussion

Results from this national sample of Medicare beneficiaries indicate that statin use in the months prior to TBI is associated with reduced in-hospital TBI mortality. Specifically, current statin use, defined as statin use in any

Table 1. Descriptive Characteristics of Statin Users and Nonusers Among Medicare Beneficiaries With TBI (N = 112 109).

Characteristics	Total Sample (N = 112 109)	Statin Use[a]		P[b]
		Statin Users (n = 45 752)	Nonusers (n = 66 357)	
Mean age (SD)	81.0 (8.1)	79.9 (7.5)	81.8 (8.2)	<.0001
Age categories, n (%)				<.0001
65-75	26 548 (23.7)	12 016 (26.3)	14 532 (21.9)	
76-85	45 064 (40.2)	20 293 (44.4)	24 771 (37.3)	
>85	40 497 (36.1)	13 443 (29.4)	27 054 (40.8)	
Sex n (%)				<.0001
Male	40 275 (35.9)	17 252 (37.7)	23 023 (34.7)	
Female	71 834 (64.1)	28 500 (62.3)	43 334 (65.3)	
Race, n (%)				.0001
White	97 316 (86.8)	39 728 (86.8)	57 588 (86.8)	
Black	6563 (5.9)	2452 (5.4)	4111 (6.2)	
Asian	3008 (2.7)	1416 (3.1)	1592 (2.4)	
Hispanic	3172 (2.8)	1325 (2.9)	1847 (2.8)	
Other[c]	2050 (1.8)	831 (1.8)	1219 (1.8)	
Median income	$49 987	$50 660	$49 518	<.0001
Geographical region, n (%)				<.0001
Midwest	28 712 (25.7)	11 505 (25.3)	17 207 (26.1)	
Northeast	23 629 (21.2)	10 111 (22.2)	13 518 (20.5)	
South	42 280 (37.9)	17 015 (37.3)	25 265 (38.2)	
West	17 010 (15.2)	6935 (15.2)	10 075 (15.3)	
Provider characteristics per 100 000 (median)				
Physicians	233.4	239.4	231.1	<.0001
Hospitals	1.6	1.6	1.7	<.0001
Hospitals with trauma services	0.2	0.2	0.2	.0631
Hospitals with neurological services	0.6	0.6	0.6	.8994
Hospital beds	301.9	300.6	303.6	<.0001
SNF stay prior to TBI[d], n (%)	7557 (6.7)	2964 (6.5)	4593 (6.9)	.0036
Chronic conditions, n (%)				
Hypertension	101 791 (90.8)	43 829 (95.8)	57 962 (87.4)	<.0001
Hyperlipidemia	84 279 (75.2)	44 251 (96.7)	40 028 (60.3)	<.0001
Ischemic heart disease	77 992 (69.6)	36 532 (79.9)	41 460 (62.5)	<.0001
Congestive heart failure	57 794 (51.6)	25 698 (56.2)	32 096 (48.4)	<.0001
Acute myocardial infarction	9969 (8.9)	6212 (13.6)	3757 (5.7)	<.0001
Valvular heart disease	10 460 (9.3)	5056 (11.1)	5404 (8.1)	<.0001
Diabetes	47 909 (42.7)	24 088 (52.7)	23 821 (35.9)	<.0001
ADRD	42 422 (37.8)	15 678 (34.3)	26 744 (40.3)	<.0001
Comorbidity burden,[e] mean (SD)	5.0 (2.3)	5.1 (2.2)	5.0 (2.3)	<.0001
Previous stroke event, n (%)	37 121 (33.1)	17 025 (37.2)	20 096 (30.3)	<.0001
TBI severity				
Mean SRRi (SD)	0.88 (0.15)	0.88 (0.15)	0.88 (0.15)	.114
Mean length of hospital stay (SD)	6.3 (8.2)	6.3 (8.8)	6.4 (7.6)	.0395

Abbreviations: TBI, traumatic brain injury; SD, standard deviation; SNF, skilled nursing facility; ADRD, Alzheimer's disease and related dementias; SRRi, independent survival risk ratio.

[a]Beneficiaries were categorized as nonusers if they did not use statins at any time within 6 months prior to TBI, while beneficiaries were categorized as users if they had any statin use at any time within 6 months prior to TBI.

[b]P value from χ^2 test for categorical variables, Student's t test for continuous variables, and Wilcoxon rank sum test to test differences between medians reflects comparison between statin users and nonusers.

[c]Other races include Native American, other, and unknown race.

[d]SNF stay in the month immediately preceding TBI.

[e]Count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD.

Table 2. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Users and Nonusers.

	Unadjusted		
	Current Use	Recent Use	Past Use
Any statin use	0.96 (0.92, 1.00)	1.10 (0.97, 1.25)	0.93 (0.78, 1.10)
Atorvastatin	0.99 (0.93, 1.06)	1.19 (1.00, 1.42)	0.82 (0.65, 1.03)
Fluvastatin	0.71 (0.49, 1.05)	0.69 (0.25, 1.91)	0.32 (0.04, 2.31)
Lovastatin	1.02 (0.91, 1.15)	1.39 (0.96, 2.01)	1.36 (0.91, 2.03)
Pravastatin	1.03 (0.91, 1.16)	0.86 (0.54, 1.38)	0.88 (0.52, 1.50)
Rosuvastatin	0.88 (0.77, 1.02)	0.60 (0.36, 1.00)	0.88 (0.54, 1.42)
Simvastatin	0.93 (0.88, 0.99)	1.03 (0.86, 1.24)	0.89 (0.71, 1.13)
	Adjusted[a]		
	Current Use	Recent Use	Past Use
Any statin use	0.87 (0.82, 0.92)	0.98 (0.84, 1.13)	0.83 (0.68, 1.01)
Atorvastatin	0.88 (0.82, 0.96)	1.14 (0.94, 1.39)	0.79 (0.61, 1.02)
Fluvastatin	0.72 (0.47, 1.11)	1.02 (0.36, 2.83)	0.39 (0.05, 2.86)
Lovastatin	0.97 (0.85, 1.12)	1.09 (0.69, 1.72)	1.24 (0.78, 1.95)
Pravastatin	0.94 (0.81, 1.08)	0.76 (0.44, 1.32)	0.61 (0.31, 1.20)
Rosuvastatin	0.79 (0.67, 0.94)	0.68 (0.39, 1.18)	0.90 (0.52, 1.55)
Simvastatin	0.84 (0.79, 0.91)	0.90 (0.73, 1.10)	0.80 (0.61, 1.04)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.
[a]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta-blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

of two months immediately preceding TBI, was linked to decreased in-hospital mortality. The decrease in mortality appears to be driven by atorvastatin, rosuvastatin, and simvastatin use, all of which are associated with a significant reduction in mortality. The greatest reduction in mortality is associated with current use of rosuvastatin (21%), followed by simvastatin (16%) and atorvastatin (12%). Fluvastatin, lovastatin, and pravastatin also are associated with decreased mortality; however, these relationships were not statistically significant. This may be due to insufficient number of beneficiaries taking these statins or channeling bias, where different treatments are given for patients with different prognoses.[22] More research is required, particularly clinical trials, to investigate the differences in mortality among statin users.

Atorvastatin, rosuvastatin, and simvastatin use in the month immediately prior to TBI was associated with decreased in-hospital mortality. This may because of the lasting impact of reduced inflammation associated with statin use. While statins' impact on lipids is apparent four to six weeks following use, there is limited research regarding statins' duration of impact on inflammation.[23] No study has examined the length of time it takes for statins to affect inflammation following TBI; however, some studies have examined secondary endpoints and inflammation associated with other chronic conditions.[24,25] One clinical trial among atherosclerosis patients found that atorvastatin treatment reduced atherosclerotic plaque inflammation starting at four weeks after treatment.[25] Another clinical trial found that simvastatin use reduced oxidative stress, which is associated with inflammation, four weeks following treatment among heart failure patients.[24] These studies indicate that, similar to its impact on lipids, statin therapy may start to affect inflammation as early as four weeks after initiation. Therefore, the reduced in-hospital mortality associated with statin therapy may be due to the lasting anti-inflammatory impact of statins as the reduction of in-hospital mortality is mainly witnessed among patients with statin use in the month immediately prior to TBI rather than several months prior to TBI.

Secondary analysis suggested that pre-TBI statin use in one or two months immediately prior to TBI may be associated with reduced 30- and 60-day mortality following injury. This, again, may be due to the lasting impact of statins' anti-inflammatory properties. However, this analysis did not adjust for medication use and other factors affecting mortality following hospitalization discharge, setting a foundation for future research to investigate the relationship between pre- and post-TBI statin use and mortality following hospitalization discharge.

Previously, three small-scale human studies have assessed the relationship between preinjury statin use and mortality survival among older adults with TBI, two studies conducted in the United States and one study in Singapore.[14,15,26] Both US studies found a significant decrease of in-hospital mortality comparing preinjury statin users to nonusers.[14,15] The third study, among Asian TBI patients, examined preinjury statin use and 14-day mortality and did not find any association between statin use and mortality.[26] However, it should be noted that all 3 of these studies were limited due to small sample sizes and nondifferentiation of statins.[14,15,26]

A major limitation of this study is the potential of the healthy user bias among statin users, meaning that healthy statin users may have been compared to less healthy nonusers.[27] Preventive therapy, such as statin therapy to prevent cardiovascular events, can exaggerate the impact of the therapy on outcomes if healthy behavior (ie, diet and exercise) are not accounted for in the analysis.[28] Statin users in particular are more likely to engage in healthy behavior.[29] Furthermore, the beneficial impact of statins on conditions including ADRD has been questioned due to a healthy user effect.[28] Unfortunately, this major limitation cannot be addressed in claims data. Another limitation is that the data only include patients hospitalized with a TBI

Table 3. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Users and Nonusers by Individual Months Prior to TBI.

	Unadjusted					
	Use in Months Prior to TBI					
	−1	−2	−3	−4	−5	−6
Any statin use	0.96 (0.92, 1.00)	0.94 (0.82, 1.08)	1.07 (0.90, 1.26)	1.15 (0.95, 1.39)	0.92 (0.72, 1.16)	0.95 (0.73, 1.22)
Atorvastatin	1.00 (0.94, 1.07)	0.89 (0.71, 1.11)	1.12 (0.71, 1.11)	1.26 (0.97, 1.62)	0.99 (0.74, 1.34)	0.64 (0.44, 0.93)
Fluvastatin	0.74 (0.50, 1.09)	0.39 (0.05, 2.84)	0.69 (1.17, 2.91)	0.69 (0.17, 2.91)	0.50 (0.07, 3.69)	NA[a]
Lovastatin	1.03 (0.91, 1.16)	0.89 (0.55, 1.44)	1.81 (1.15, 2.84)	0.92 (0.48, 1.75)	1.40 (0.82, 2.40)	1.31 (0.72, 2.38)
Pravastatin	1.04 (0.92, 1.18)	0.87 (0.53, 1.43)	0.73 (0.37, 1.43)	1.03 (0.54, 1.98)	0.63 (0.28, 1.43)	1.22 (0.61, 2.43)
Rosuvastatin	0.83 (0.71, 0.97)	1.44 (0.98, 2.10)	0.46 (0.21, 0.98)	0.79 (0.40, 1.56)	1.21 (0.68, 2.14)	0.51 (0.21, 1.26)
Simvastatin	0.93 (0.88, 0.99)	0.93 (0.77, 1.14)	1.00 (0.78, 1.27)	1.08 (0.82, 1.42)	0.71 (0.50, 1.01)	1.11 (0.81, 1.51)
	Adjusted[b]					
	Use in Months Prior to TBI					
	−1	−2	−3	−4	−5	−6
Any statin use	0.89 (0.84, 0.94)	0.84 (0.71, 0.98)	0.98 (0.81, 1.18)	0.98 (0.79, 1.23)	0.86 (0.66, 1.12)	0.81 (0.61, 1.08)
Atorvastatin	0.91 (0.84, 0.99)	0.74 (0.57, 0.96)	0.18 (0.90, 1.53)	1.12 (0.83, 1.50)	0.98 (0.70, 1.36)	0.60 (0.40, 0.91)
Fluvastatin	0.74 (0.47, 1.15)	0.63 (0.08, 4.67)	0.95 (0.22, 4.04)	1.06 (0.25, 4.52)	0.58 (0.08, 4.40)	N/A[a]
Lovastatin	1.01 (0.87, 1.16)	0.72 (0.40, 1.28)	1.17 (0.65, 2.09)	1.01 (0.49, 2.09)	1.43 (0.80, 2.56)	1.03 (0.50, 2.14)
Pravastatin	0.97 (0.84, 1.12)	0.83 (0.48, 1.44)	0.79 (0.39, 1.62)	0.73 (0.32, 1.67)	0.36 (0.12, 1.07)	1.00 (0.43, 2.34)
Rosuvastatin	0.74 (0.62, 0.89)	1.54 (1.00, 2.37)	0.54 (0.24, 1.23)	0.88 (0.42, 1.85)	1.10 (0.55, 2.21)	0.68 (0.27, 1.71)
Simvastatin	0.86 (0.80, 0.92)	0.86 (0.69, 1.08)	0.89 (0.68, 1.18)	0.91 (0.66, 1.25)	0.68 (0.46, 1.02)	0.94 (0.65, 1.34)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.

[a]Estimate too small and unreliable.

[b]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta-blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

Table 4. ORs (95% CIs) of 30-Day and 60-Day Mortality Following TBI Comparing Current Statin Users and Nonusers.

	Unadjusted		Adjusted[a]	
	30-Day Mortality	60-Day Mortality	30-Day Mortality	60-Day Mortality
Statins				
Atorvastatin	0.83 (0.77, 0.89)	0.80 (0.71, 0.90)	0.90 (0.83, 0.97)	0.88 (0.78, 1.00)
Rosuvastatin	0.60 (0.50, 0.72)	0.62 (0.47, 0.82)	0.72 (0.60, 0.87)	0.75 (0.56, 0.99)
Simvastatin	0.78 (0.73, 0.83)	0.82 (0.74, 0.91)	0.84 (0.78, 0.90)	0.87 (0.78, 0.97)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.

[a]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100,000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

and exclude patients with less severe TBIs who did not experience a hospitalization. While this limitation cannot be overcome within the data, sensitivity analysis was conducted by excluding beneficiaries who died within 24 hours of hospitalization, as this is indicative of most severe TBI.[14,15] Similarly, the administrative nature of the data made it impossible to capture injury severity, which could have been possible with medical chart reviews. However, injury severity was ascertained through the ICD-9-CM code-based SRRi.

Last, the data do not capture medication usage during TBI hospitalization; medications given in-hospital that may improve survival could not be adjusted in the analysis. However, it is not known whether statins were continued during hospitalization. However, one study examined statin discontinuation during TBI hospitalization and found that 39% of pre-TBI statin users did not receive statins within 48 hours of hospitalization.[30] Of those that discontinued, 58% discontinued due to severity of injury.[30] It is unclear why nonsevere patients discontinued statins; however, it may be due to medical oversight.[30] Future studies can further investigate statin discontinuation rates while hospitalized and explore potential reasons for discontinuation.

There also are numerous strengths of this study. This is the first large-scale observational study assessing pre-TBI statin use and mortality. This study also was able to include a myriad of covariates from CCW and AHRF data to reduce bias. Adjusting for these covariates helped reduce confounding associated with beneficiary health, sociodemographic, and geographical characteristics. Additionally, a strength of this study is the large sample that allowed sensitivity analysis to assess the robustness of the results by excluding beneficiaries who died within 24 hours of hospitalization. The results from the sensitivity analyses supported primary analyses indicating that current use of atorvastatin, rosuvastatin, and simvastatin and use in the month immediately prior to TBI significantly reduced in-hospital TBI mortality. Furthermore, sensitivity analysis regarding the impact of statin dose on mortality showed similar results.

Conclusion

More research is required examining the impact of statin duration in older TBI patients to corroborate the results of this study. However, the results of this study make an important contribution for clinicians treating older adults with TBI. They indicate that with atorvastatin, rosuvastatin, or simvastatin use, there may be potential to reduce the death rate among older adults who suffer a TBI.

The current translational research has serious implications for health care providers. Clinicians can encourage adherence to statin therapy for patients with CVD to not only treat CVD but also to potentially reduce the risk of mortality in the event of a TBI. Additionally, among patients with preinjury statin use, health care providers can look to continue statin use during hospitalization if appropriate, to avoid any lapse in statin treatment. Discontinuing statins in hospital after injury may have deleterious effects on mortality; however, it is unknown if beneficiaries discontinued statins during hospitalization in this study.[30] Furthermore, given the possibility of healthy user bias there is a need for quality clinical trials investigating the impact of statin use in-hospitalization and mortality. This study can be used to help clinicians and patients make informed health care decisions and as a stepping stone for future research.

Appendix

Appendix Table 1. Frequency of Statin Use Among Medicare Beneficiaries Prior to TBI.

	Statin Use			
	Current Use	Recent Use	Prior Use	Any Use
Any statin use	41 174	2852	930	45 752
Atorvastatin	13 156	1370	1071	15 597
Fluvastatin	437	64	34	535
Lovastatin	3432	273	235	3940
Pravastatin	3266	249	192	3707
Rosuvastatin	2653	293	231	3177
Simvastatin	19 194	1440	964	21 598

Abbreviation: TBI, traumatic brain injury.

Appendix Table 2. Frequency of Atorvastatin, Rosuvastatin, and Simvastatin Doses per Month, 2 Months Prior to TBI.

	Use in Months Prior to TBI	
Statin Doses[a]	−1	−2
Atorvastatin, n (%)		
≤10 mg	4672 (39.8)	4811 (40.2)
>10 mg to ≤20 mg	3833 (32.7)	3883 (32.4)
>20 mg to ≤40 mg	2301 (19.6)	2341 (19.6)
>40 mg	920 (7.9)	940 (7.9)
Rosuvastatin, n (%)		
≤5 mg	510 (21.3)	492 (20.3)
>5 mg to ≤10 mg	1187 (49.6)	1235 (51.0)
>10 mg to ≤20 mg	510 (21.3)	511 (21.1)
>20 mg	184 (7.7)	185 (7.6)
Simvastatin, n (%)		
≤10 mg	1682 (10.7)	1641 (10.6)
>10 mg to ≤20 mg	6297 (40.2)	6197 (40.1)
>20 mg to ≤40 mg	6055 (38.7)	5997 (38.8)
>40 mg	1625 (10.4)	1609 (10.4)

Abbreviation: TBI, traumatic brain injury.
[a]Beneficiaries only had one dose per month. Dose for beneficiaries that changed doses within a month were averaged to get a single dose.

Appendix Table 3. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Doses Among Atorvastatin, Rosuvastatin, or Simvastatin Users Prior to TBI.

	Unadjusted		Adjusted[a]	
	Use in Months Prior to TBI		Use in Months Prior to TBI	
	−1	−2	−1	−2
Atorvastatin				
≤10 mg	Reference	Reference	Reference	Reference
>10 mg to ≤20 mg	1.01 (0.87, 1.18)	0.98 (0.84, 1.15)	1.05 (0.88, 1.25)	1.01 (0.85, 1.20)
>20 mg to ≤40 mg	1.08 (0.90, 1.28)	1.05 (0.88, 1.25)	1.03 (0.83, 1.26)	0.95 (0.78, 1.17)
>40 mg	1.13 (0.89, 1.44)	1.04 (0.81, 1.33)	1.03 (0.77, 1.37)	0.89 (0.66, 1.19)
Rosuvastatin				
≤5 mg	Reference	Reference	Reference	Reference
>5 mg to ≤10 mg	0.93 (0.63, 1.39)	0.89 (0.60, 1.30)	0.91 (0.56, 1.47)	0.90 (0.57, 1.44)
>10 mg to ≤20 mg	1.03 (0.65, 1.64)	1.01 (0.65, 1.58)	0.62 (0.34, 1.14)	0.65 (0.36, 1.16)
>20 mg	1.02 (0.54, 1.94)	1.04 (0.57, 1.91)	0.89 (0.40, 1.98)	0.90 (0.42, 1.90)
Simvastatin				
≤10 mg	Reference	Reference	Reference	Reference
>10 mg to ≤20 mg	0.83 (0.69, 0.99)	0.85 (0.70, 1.02)	0.78 (0.63, 0.96)	0.79 (0.63, 0.97)
>20 mg to ≤40 mg	0.80 (0.66, 0.96)	0.84 (0.69, 1.01)	0.72 (0.58, 0.89)	0.73 (0.59, 0.91)
>40 mg	0.74 (0.58, 0.94)	0.81 (0.64, 1.04)	0.66 (0.50, 0.88)	0.71 (0.54, 0.94)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.
[a]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta-blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

Appendix Table 4. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Users and Nonusers Among Beneficiaries That Died Within 24 Hours of Hospitalization (n = 110 970).

	Unadjusted		
	Current Use	Recent Use	Past Use
Any statin use	0.95 (0.91, 1.00)	1.08 (0.95, 1.24)	0.92 (0.76, 1.10)
Atorvastatin	0.99 (0.92, 1.06)	1.16 (0.96, 1.40)	0.77 (0.60, 0.99)
Fluvastatin	0.69 (0.46, 1.04)	0.79 (0.29, 2.16)	0.36 (0.05, 2.61)
Lovastatin	1.00 (0.88, 1.14)	1.37 (0.93, 2.03)	1.37 (0.89, 2.08)
Pravastatin	1.04 (0.92, 1.19)	0.82 (0.50, 1.36)	0.80 (0.45, 1.44)
Rosuvastatin	0.86 (0.73, 1.00)	0.55 (0.32, 0.96)	0.88 (0.53, 1.47)
Simvastatin	0.93 (0.88, 0.99)	1.04 (0.85, 1.24)	0.91 (0.71, 1.16)
	Adjusted[a]		
	Current Use	Recent Use	Past Use
Any statin use	0.87 (0.82, 0.92)	0.98 (0.84, 1.15)	0.82 (0.67, 1.01)
Atorvastatin	0.88 (0.81, 0.95)	0.13 (0.92, 1.40)	0.73 (0.55, 0.97)
Fluvastatin	0.67 (0.42, 1.07)	1.10 (0.39, 3.06)	0.42 (0.06, 3.14)
Lovastatin	0.96 (0.83, 1.11)	1.07 (0.67, 1.72)	1.26 (0.79, 2.02)
Pravastatin	0.94 (0.82, 1.09)	0.75 (0.42, 1.33)	0.50 (0.24, 1.07)
Rosuvastatin	0.76 (0.64, 0.91)	0.62 (0.34, 1.14)	0.88 (0.49, 1.57)
Simvastatin	0.85 (0.79, 0.91)	0.90 (0.72, 1.12)	0.81 (0.62, 1.07)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.

[a]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

Appendix Table 5. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Users and Nonusers, by Individual Months Prior to TBI Among Beneficiaries Who Did Not Die Within 24 Hours of Hospitalization (n = 110 970).

	Unadjusted					
	Use in Months Prior to TBI					
	−1	−2	−3	−4	−5	−6
Any statin use	0.95 (0.91, 1.00)	0.93 (0.80, 1.08)	1.05 (0.88, 1.25)	1.13 (0.88, 1.25)	0.92 (0.72, 1.18)	0.91 (0.69, 1.19)
Atorvastatin	1.00 (0.93, 1.08)	0.82 (0.64, 1.05)	1.12 (0.87, 1.45)	1.20 (0.91, 1.59)	0.98 (0.72, 1.35)	0.55 (0.36, 0.84)
Fluvastatin	0.71 (0.47, 1.08)	0.44 (0.06, 3.21)	0.79 (0.19, 3.29)	0.79 (1.19, 3.29)	0.56 (0.08, 4.17)	N/A[a]
Lovastatin	1.01 (0.88, 1.15)	0.95 (0.58, 1.56)	1.68 (1.02, 2.75)	1.04 (0.54, 1.98)	1.37 (0.77, 2.44)	1.35 (0.73, 2.53)
Pravastatin	1.05 (0.92, 1.20)	0.98 (0.60, 1.61)	0.73 (0.36, 1.50)	0.94 (0.46, 1.92)	0.47 (0.17, 1.28)	1.23 (0.59, 2.54)
Rosuvastatin	0.82 (0.69, 0.96)	1.24 (0.81, 1.91)	0.44 (0.20, 1.00)	0.70 (0.33, 1.49)	1.26 (0.69, 2.28)	0.47 (0.17, 1.26)
Simvastatin	0.93 (0.87, 0.99)	0.96 (0.78, 1.18)	0.97 (0.75, 1.26)	1.10 (0.82, 1.46)	0.73 (0.51, 1.06)	1.11 (0.80, 1.54)

(continued)

Appendix Table 5. (continued)

	Adjusted[b]					
	Use in Months Prior to TBI					
	−1	−2	−3	−4	−5	−6
Any statin use	0.89 (0.84, 0.94)	0.84 (0.71, 0.99)	0.97 (0.79, 1.18)	1.01 (0.80, 1.28)	0.87 (0.66, 1.14)	0.78 (0.57, 1.06)
Atorvastatin	0.91 (0.84, 0.99)	0.71 (0.54, 0.93)	1.16 (0.88, 1.53)	1.12 (0.82, 1.53)	0.94 (0.66, 1.33)	0.53 (0.33, 0.84)
Fluvastatin	0.68 (0.42, 1.10)	0.69 (0.09, 5.11)	1.02 (0.24, 4.34)	1.16 (0.27, 4.93)	0.64 (0.09, 4.89)	N/A[a]
Lovastatin	0.98 (0.85, 1.14)	0.79 (0.44, 1.41)	1.05 (0.57, 1.96)	1.11 (0.54, 2.30)	1.44 (0.78, 2.64)	1.08 (0.51, 2.26)
Pravastatin	0.97 (0.83, 1.12)	0.90 0.52, 1.55)	0.77 (0.36, 1.64)	0.73 (0.31, 1.73)	0.21 (0.05, 0.84)	0.94 (0.38, 2.30)
Rosuvastatin	0.72 (0.60, 0.87)	1.30 (0.81, 2.09)	0.49 (0.20, 1.20)	0.81 (0.36, 1.83)	1.08 (0.53, 2.23)	0.65 (0.24, 1.79)
Simvastatin	0.86 (0.80, 0.93)	0.89 (0.71, 1.11)	0.88 (0.66, 1.18)	0.93 (0.67, 1.30)	0.71 (0.47, 1.07)	0.94 (0.64, 1.36)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.

[a]Estimate too small and unreliable.

[b]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta-blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

Appendix Table 6. ORs (95% CIs) of In-Hospital Mortality Following TBI Comparing Statin Doses Among Atorvastatin, Rosuvastatin, or Simvastatin Users Prior to TBI Among Beneficiaries That Died Within 24 Hours of Hospitalization.

	Unadjusted		Adjusted[a]	
	Use in Months Prior to TBI		Use in Months Prior to TBI	
	−1	−2	−1	−2
Atorvastatin				
≤10 mg	Reference	Reference	Reference	Reference
>10 mg to ≤20 mg	1.01 (0.86, 1.19)	1.00 (0.85, 1.17)	1.05 (0.87, 1.26)	1.01 (0.84, 1.22)
>20 mg to ≤40 mg	1.11 (0.92, 1.34)	1.07 (0.89, 1.29)	1.05 (0.85, 1.30)	0.97 (0.78, 1.20)
>40 mg	1.12 (0.87, 1.45)	1.05 (0.81, 1.36)	1.06 (0.78, 1.43)	0.93 (0.68, 1.25)
Rosuvastatin				
≤5 mg	Reference	Reference	Reference	Reference
>5 mg to ≤10 mg	0.99 (0.64, 1.53)	0.96 (0.63, 1.46)	0.90 (0.54, 1.51)	0.99 (0.60, 1.64)
>10 mg to ≤20 mg	1.07 (0.64, 1.77)	1.08 (0.66, 1.76)	0.67 (0.35, 1.27)	0.76 (0.41, 1.42)
>20 mg	1.25 (0.65, 2.41)	1.29 (0.69, 2.41)	1.06 (0.47, 2.40)	1.16 (0.53, 2.50)
Simvastatin				
≤10 mg	Reference	Reference	Reference	Reference
>10 mg to ≤20 mg	0.83 (0.69, 1.01)	0.86 (0.70, 1.05)	0.79 (0.64, 0.99)	0.80 (0.64, 1.00)
>20 mg to ≤40 mg	0.79 (0.65, 0.96)	0.83 (0.68, 1.02)	0.72 (0.58, 0.91)	0.74 (0.59, 0.93)
>40 mg	0.78 (0.61, 1.01)	0.84 (0.65, 1.09)	0.72 (0.54, 0.96)	0.76 (0.57, 1.02)

Abbreviations: OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; CHF, congestive heart failure; AMI, acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease; ADRD, Alzheimer's disease and related dementias; SNF, skilled nursing facility; SRRi, independent survival risk ratio.

[a]Adjusted for demographic characteristics (age, sex, race, income, region); medications (antiplatelets, anticoagulants, beta-blockers, other statins); cardiovascular disease (CHF, AMI, IHD, VHD, hyperlipidemia, hypertension, prior stroke); diabetes; Alzheimer's disease and related dementia; count of CCW chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD; SNF stay in month prior to TBI; injury severity (SRRi, length of hospital stay); provider and hospital characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds).

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