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11-1-2018

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Abstract

Objective—To assess the relationship between post-TBI statin use and: 1) mortality; and 2) the incidence of associated morbidities, including stroke, depression, and Alzheimer's disease and related dementias (ADRD) following injury.

Setting and Participants—Nested-cohort of all Medicare beneficiaries 65 and older who survived a TBI hospitalization during 2006 through 2010. The final sample comprised 100,515 beneficiaries.

Design—Retrospective cohort study of older Medicare beneficiaries. Relative risks (RR) and 95% confidence interval (CI) were obtained using discrete time analysis and generalized estimating equations.

Measures—The exposure of interest included monthly atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin use. Outcomes of interest included mortality, stroke, depression, and ADRD.

Results—Statin use of any kind was associated with decreased mortality following TBI-hospitalization discharge. Any statin use also was associated with a decrease in any stroke (RR, 0.86; 95% confidence intervals (CI), 0.81, 0.91), depression (RR, 0.85; 95% CI, 0.79, 0.90), and ADRD (RR, 0.77; 95% CI, 0.73, 0.81).

Conclusion—These findings provide valuable information for clinicians treating older adults with TBI as clinicians can consider, when appropriate, atorvastatin and simvastatin to older adults with TBI in order to decrease mortality and associated morbidities.

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Conflicts of Interest

For the remaining authors none were declared.

The authors declare no conflicts of interest.

Keywords

Traumatic brain injury; statins; mortality; TBI sequelae; Medicare; older adults

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Traumatic brain injury (TBI) impacts millions of adults in the US and accounts for almost one-third of all injury-related deaths.[1] The rates of TBI-related hospitalizations and deaths is highest among adults 65 years of age and older, and TBI mortality rates are estimated at 24.5, 51.4, and 103.8 per 100,000 for adults aged 65–74, 75–84, and 85 and older, respectively.[1,2]

In addition to an increase in mortality for older adults, there also is a chronic neuroinflammation following injury. This sustained inflammatory cascade can potentially lead to several unfavorable outcomes including stroke, depression, and Alzheimer's disease and related dementias (ADRD) and studies have indicated these associations.[3–8] These sequelae of TBI can occur in the days, months, and years following TBI.[4,9,10] It should be noted that while these morbidities are linked to TBI, these morbidities can occur naturally among older adults as aging also contributes to chronic neuroinflammation. Therefore, older adults with TBI are particularly susceptible to both chronic neuroinflammation and ensuing sequelae of TBI.[4]

Pharmacotherapy guidelines for TBI have focused largely on treating acute injury, aimed to reduce pain and intracranial pressure.[11,12] Since TBI is typically followed by associated morbidities, pharmacological treatment also may be geared toward alleviating symptoms of these associated morbidities.[13,14]

The Operation Brain Trauma Therapy (OBTT) consortium was established to highlight acute and long-term potential pharmacotherapies for TBI.[15] The consortium has suggested statins, typically used to treat cardiovascular disease (CVD), as a potential therapy for TBI and its sequelae because statins may help to reduce chronic neuroinflammation and increase cerebral blood flow following TBI.[15,16]

No study has investigated the relationship between statin use following TBI and mortality or associated morbidities. Thus, the primary objective of this study is to assess the relationship between post-TBI statin use mortality. A secondary objective is to examine the relationship between post-TBI statin use and the development of TBI sequelae, including stroke, depression, and ADRD among older Medicare beneficiaries.

Methods

Study Sample

The Chronic Condition Data Warehouse (CCW) from the Centers for Medicare and Medicaid Services was used to investigate the relationship between post-TBI statin use and mortality or associated morbidities following TBI. TBI was identified by inpatient claims using the 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. Beneficiaries' first admission date for TBI during this time period is defined as

the index date/index TBI. Any TBI occurring within 14 days of a previous TBI was collapsed and classified as a single TBI event due to the possibility of multiple TBI claims within 14 days being for the care for a single TBI event.[6,7]

Beneficiaries were required to be at least 65 years of age at the time of TBI, have six months of observation time prior to TBI, and continuous coverage of Medicare Parts A, B, and D throughout the study period following TBI. Therefore, beneficiaries could have up to 54 months of follow-up. Beneficiaries with Medicare Part C (private insurance) were excluded because their inpatient, outpatient, and medication claims were not available.

Exposure

The exposure of interest was use of statins, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Individual and any statin use was determined per 30-day period (henceforth referred to as month) prior to and following TBI. Beneficiaries were required to have either a claim for a filled statin prescription or a proportion of days covered (PDC) of greater than 0 in a month to be classified as statin users in a particular month. This approach has previously been used in pharmacoepidemiology studies using Medicare claims data.[17,18] PDC was calculated by dividing the number of days' supply a statin was available during a month by the number of days in a month (30). Since beneficiaries had six months of coverage prior to TBI, pre-TBI statin use was divided into four categories: 1) use in the first or second month immediately prior to TBI; 2) use that was three or four months prior to TBI; 3) use that was over four months prior to TBI; and 4) no use prior to TBI. Following TBI, beneficiaries were classified as users or non-users on a monthly basis, creating a time-varying exposure.

Outcomes

The two outcomes of interest included mortality and TBI sequelae (stroke, depression, or ADRD). While there are several morbidities associated with TBI, this study focused on stroke, depression, and ADRD. These associated morbidity outcomes are studied due to their prevalence and ease of identification in claims data. Mortality was assessed following hospital discharge, making the outcome all-cause mortality rather than TBI-specific. Different variables were created to assess 30-day, 60-day, 90-day and mortality at any time following TBI hospitalization discharge. The 30-day, 60-day, and 90-day mortality variables were mutually exclusive in order to examine the time period for when statin use may have been protective for primary injury. Beneficiaries who died within 30 days were excluded when analyzing 60-day or 90-day mortality to avoid biasing the results.

Stroke was defined by inpatient claims using ICD-9 codes 430.xx–432.xx (hemorrhagic stroke) and 433.xx, 434.xx, 435.xx, 437.0x, 437.1x (ischemic stroke). Depression and ADRD were defined through the CCW flags for chronic conditions. Beneficiaries with their first diagnosis of depression or ADRD following TBI were flagged as having incident depression or ADRD, respectively.

Covariates

This study incorporated covariates including sociodemographic, health, drug utilization, and geographical characteristics using CCW and Area Health Resource File (AHRF) data. CCW data included demographic characteristics, chronic conditions, and injury severity. Injury severity covariates included length of hospital stay (LOS), discharge status, and TBI injury severity, determined by the ICD-9-CM based independent survival risk ratio (SRRi) measure.

In addition to pre-TBI statin use, drug utilization covariates included anticoagulant, antiplatelet, and beta-blocker use per month following TBI. These pharmacotherapies were included because they may impact mortality and associated morbidities, or have been indicated as potential treatments for TBI.[19–22]

AHRF data was linked to CCW data by beneficiaries' county codes and included demographic variables such as income and region, and healthcare provider characteristics such as total number of physicians, hospitals, and beds.[23]

Data Analysis

Bivariate analysis examining associations between statin use and demographic, health, and geographic characteristics were tested using chi-squared test of proportions for categorical variables, Student's t-tests for continuous variables, and the Wilcoxon Rank Sum test when comparing medians between statin users and non-users.

Given the longitudinal nature of the data, discrete time analysis was used to assess the relationship between statin use and mortality and associated morbidities. This relationship was assessed using generalized estimating equations (GEE) with a binomial distribution and complimentary log-log link. This modelling approach is appropriate for survival analysis given multiple observations per beneficiary and a time-varying exposure.[24]

Statin use was lagged one month for TBI sequelae outcomes to ensure the exposure preceded the outcome.[18,24] Statin use was not lagged for the mortality models because observation time for beneficiaries ends at death; therefore, mortality will always follow the exposure. This is not necessarily true for beneficiaries who experience TBI sequelae events because beneficiaries are censored following the month an event is experienced. For instance, it is possible that a beneficiary experiences an event in the beginning of the month, and continues to receive statins in the same month following the event. In such cases, without lagging, the outcome precedes the exposure. Separate GEE models were used for each outcome and each beneficiary was censored after experiencing the outcome of interest.

All final models included sociodemographic variables (age, race, sex, county-level income, low income subsidy (LIS) per month, and region); comorbidities (hyperlipidemia, hypertension, congestive heart failure, ischemic heart disease, acute myocardial infarction, ADRD, valvular heart disease, and diabetes); count of CCW chronic conditions, excluding the above mentioned comorbidities due to their relationship with the exposure and outcomes; history of stroke; injury severity (LOS, discharge status, SRRi); healthcare provider characteristics (total physicians, hospitals, hospitals with trauma services, hospitals

with neurological services, and beds per 100,000 people); and pre-TBI statin use. The mortality and stroke models also included anticoagulant, antiplatelet, and beta-blocker use in the month due to their relationship with statin use and mortality and stroke.[19–22] Additionally, the model assessing any stroke included history of any stroke in the six months prior to TBI. Similarly, the models assessing ischemic and hemorrhagic stroke included history of ischemic and hemorrhagic stroke, (respectively), six months prior to TBI. Lastly, the depression model also included monthly beta-blocker use.

Secondary analyses on associated morbidities were conducted after excluding beneficiaries with less than 12 months of observation time following TBI. This was done to allow beneficiaries greater time to experience or be diagnosed with TBI sequelae events. Sensitivity analyses were conducted by including inverse probability of treatment weights (IPTW). IPTW help decrease bias caused by non-random assignment of treatment.[25] IPTWs were constructed by modelling any post-TBI statin use following hospitalization discharge as a function of the risk factors (baseline and time-varying) for the outcomes of interest. The risk factors included the covariates mentioned above for each model. The final sensitivity analysis models included their IPTW in addition to their individual covariates IPTW.

Relative risks (RR) and 95% confidence intervals (CI) were reported. All analyses were performed using SAS (Cary, North Carolina). This study was approved by the Institutional Review Board of the University of Maryland Baltimore.

Results

A total of 116,170 Medicare beneficiaries 65 and older were hospitalized with a TBI from 2006 through 2010. Of these, 110,500 had six months of observation time prior to TBI and continuous Medicare Parts A, B, and D coverage following TBI. The final sample comprised 100,515 beneficiaries who survived TBI hospitalization. Approximately 50% (50,173) of these beneficiaries used statins either prior to and/or following TBI.

The study sample was predominately white (87%) and female (65%) and the mean age of the sample was 81 years of age (standard deviation (SD), 8.1). Statin users were more likely to have CVD (p < 0.0001). While 93% of statin users had hyperlipidemia, the majority (57%) of non-users also had hyperlipidemia (p < 0.0001) (Table 1).

Statin use remained stable throughout the study period. The most commonly used statin was simvastatin, followed by atorvastatin while fluvastatin was the least used statin (results not shown).

A total of 41,650 beneficiaries died following TBI hospitalization discharge, of whom 8,507 died within 30 days, 3,348 died after 30 days but within 60 days, and 2,439 died after 60 days but within 90 days of hospitalization discharge. A total of 9,420 beneficiaries developed ischemic stroke, 3,841 had hemorrhagic stroke, 10,748 had incident depression and 14,907 had incident ADRD.

Adjusted GEE models showed that post-TBI statin use of any kind was associated with lower mortality following TBI-hospitalization discharge. The greatest difference is seen in 30-day mortality following TBI (Table 2).

Adjusted analysis of associated morbidities indicated that any statin use was associated with a lower risk of any stroke (RR, 0.86; 95% CI, 0.81, 0.91), ischemic stroke (RR, 0.91; 95% CI, 0.85, 0.96), hemorrhagic stroke (RR, 0.75; 95% CI, 0.67, 0.83), depression (RR, 0.85; 95% CI, 0.79, 0.90), and ADRD (RR, 0.77; 95% CI, 0.73, 0.81). Both atorvastatin and simvastatin use were associated with a lower risk of all associated morbidity outcomes (Table 3). Secondary analysis among beneficiaries with at least 12 months of observation time following TBI showed similar associations (Table 4).

Sensitivity analyses incorporating IPTW also showed similar results for mortality and associated morbidities (see Tables 1–3, Supplementary material).

Discussion

This is the first study to investigate the relationship of statin use following TBI and mortality and associated morbidities post TBI-hospitalization discharge. In this sample of older Medicare beneficiaries with TBI, statin use following injury was associated with major decreases in 30-day, 60-day, and 90-day mortality, as well as a reduction in ischemic and hemorrhagic stroke, incident depression, and ADRD. Specifically, atorvastatin and simvastatin were associated with significant decreases in all TBI sequelae outcomes. The decrease in mortality and associated morbidities may be due to statins' anti-inflammatory properties. Furthermore, these statins were the most commonly used statins. These results are especially encouraging because statin users were more likely to have illnesses prior to TBI, such as history of stroke, and can be viewed as having higher risk of mortality and associated morbidities. However, even with a history of stroke and other CVD, these beneficiaries witnessed lower mortality and TBI sequelae events.

One study previously examined the association with statin discontinuation during hospitalization and found that statin discontinuation among pre-injury statin users was associated with an approximately four-fold higher mortality than patients that continued statin use during hospitalization.[26] However, this relationship was not significant (p=0.055), potentially due to their small sample size (n=61).[26] Another study of 39 TBI patients, of which 19 received statins for ten days following TBI, assessed the impact of statin on inflammation, rather than mortality. The results of this study indicated that statin use decreased inflammation following TBI.[27]

This is also the first study to investigate the relationship between statin use following TBI and TBI sequelae, including stroke, depression, and ADRD. The results indicate that any statin use was associated with 9% lower risk of ischemic stroke, 25% lower risk of hemorrhagic stroke, and 14% lower risk of any stroke, controlling for pre-TBI comorbidity. Atorvastatin and simvastatin were the only statins associated with lower risk of both ischemic and hemorrhagic stroke. One study among older Medicare beneficiaries compared rates of ischemic and hemorrhagic prior to and following TBI and found that rate of

ischemic stroke following TBI was 1.3 times greater than pre-TBI and the rate of hemorrhagic stroke following TBI was 6.5 times greater than pre-TBI.[6] The greater increase in the rate of hemorrhagic stroke make the findings from this study especially encouraging as statin use is associated with significantly lower risk of hemorrhagic stroke. It should be noted that statins are often used among stroke patients; the results of this study suggests that statins also may be beneficial for individuals at risk of stroke following TBI.

All statins except fluvastatin were associated with lower incident depression and ADRD following TBI. These statins were all associated at least 15% lower incident depression and at least 17% lower incident ADRD. One study examined the rates of depression among older Medicare beneficiaries with TBI and found the rates of depression almost doubled following TBI.[7] Furthermore, moderate and severe TBI also has been linked to a 2.3 and 4.5 times increase in the risk of ADRD, respectively, as TBI can hasten the natural cognitive decline among older adults.[28,29] The increase in the risk of depression and ADRD following TBI is partially due to chronic neuroinflammation, which is a common physiological consequence of TBI.[4,5,30] However, it should be acknowledged that the association between TBI and late life neurodegenerative conditions such as ADRD has been questioned, requiring further investigation of the association between TBI and ADRD. [31]

While this is the first study to investigate the relationship between statin use following TBI and post-TBI hospitalization discharge mortality and associated morbidities, it is not without limitations. Primarily, the mortality observed in this study is all-cause mortality rather than mortality related to complications of TBI. The CCW data does not indicate cause of death. However, we examined multiple mortality models in which the relationship between 30-day, 60-day, and 90-day mortality and statin use was assessed. It is possible that 30-day mortality is more likely to be TBI-specific than other mortality models and it is in this model that beneficiaries witnessed the greatest difference in mortality. Additionally, it is possible that beneficiaries discontinued statin use during end-of-life care and died a few months following discontinuation. This analysis classifies such beneficiaries as non-users at the time of death, potentially artificially inflating the impact of statin use on mortality. Similarly, statins could have only been prescribed to less severe TBI patients with a greater anticipated life expectancy, as compared to more severe patients with a decreased life expectancy. This healthy user effect may have biased the results as healthy statin users were potentially compared to less healthy non-users.[32] Lastly, potentially life-saving medications given during hospitalization or medications taken over the counter, such as non-steroidal anti-inflammatory drugs are not available in the data, and could not be accounted for in the analysis. Furthermore, other medications available in the data that could impact associated outcomes were not included in the analysis. However, this was done in order to build parsimonious models. For instance, antidepressants were not included because they are correlated with depression, which was included as a count of comorbidities.

Another limitation is that depression is episodic as beneficiaries may experience relapses from remission, therefore they may be misclassified as depressed or non-depressed.[33] To counter this limitation, in the examination of depression as an outcome, beneficiaries with a prior CCW diagnosis of depression were excluded. This helped in creating a cleaner cohort in which beneficiaries did not have prevalent depression, and therefore mitigating possible

misclassification. Similarly, in the examination of ADRD as an outcome, beneficiaries with prior ADRD were excluded from the analysis. However, it was not possible to exclude beneficiaries with undiagnosed depression and ADRD prior to TBI.

There are multiple strengths to this study. The longitudinal study design allowed for the assessment of a time-varying exposure, which mimics a "real-world" setting. This study also was able to differentiate the impact between statins. Additionally, this study was able to incorporate several covariates by linking CCW and AHRF data. Including sociodemographic, health, drug utilization, and geographical covariates helped reduce confounding. Furthermore, sensitivity analysis with IPTW was incorporated to reduce selection bias.

While this study had methodological strengths, the most salient strength of this study is that it provides precious information regarding statin use and outcomes following TBI. No prior study has investigated the relationship between statin use following TBI and mortality and associated morbidities. Previous animal studies have examined secondary endpoints such as neuroinflammation and other biomarkers and have found that statin use following TBI decreases neuroinflammation and improves neurological function following injury.[34–42] It should be noted that some previous human clinical trials have failed after encouraging results from animal studies, potentially due to inadequate biomarkers.[43] However, this translational retrospective study sets the platform for human clinical trial by examining primary endpoints. Unlike previous studies human clinical trials examining pharmacologic treatments for TBI following encouraging animal research, future clinical trials investigating the impact of statins on TBI patients can utilize the information gained from this large observational study.

This large-scale study of older Medicare beneficiaries highlights the potential of statins to treat mortality and associated morbidities associated with TBI. The study found that atorvastatin and simvastatin are not only the most commonly used statins, but are also the only two statins that were associated with a significant risk lowering in all outcomes observed. Findings provide valuable information for clinicians treating older adults with TBI. As this study finds, the majority of non-statin users had also had hyperlipidemia and clinicians can consider, when appropriate, statin use among elderly TBI patients with and without hyperlipidemia. While this study provides a foundation, more research is required to investigate mortality and associated morbidities associated with TBI in order to corroborate these results. Future research can incorporate non-TBI patients to clarify the benefits of statins specifically to TBI. Furthermore, future research can examine other salient associated morbidities following TBI in order to provide a clearer sense of range of sequelae associated with TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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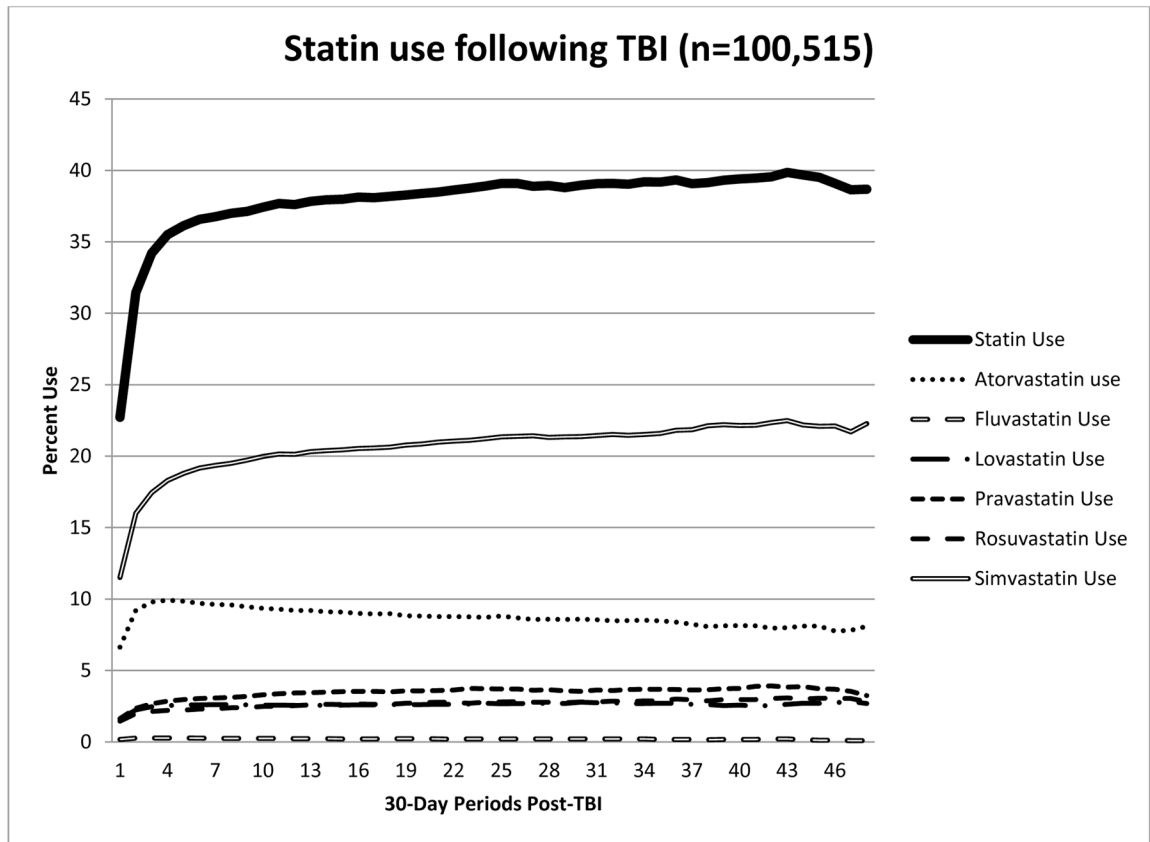
Figure 1.
Statin use per month relative to TBI among older Medicare beneficiaries (n = 100,515)

Table 1

Descriptive characteristics of statin users and non-users (n=100,515)

Characteristics	Total Sample (n=100,515)	Statin Use [a]		P-value [b]
		Statin Users (n=50,173)	Non-Users (n=50,342)	
Mean Age (SD)	81.0 (8.1)	79.6 (7.5)	82.5 (8.3)	<0.0001
Age Categories No. (%)				<0.0001
65–75	23,908 (23.8)	13,961 (27.8)	9,947 (19.8)	
76–85	40,350 (40.1)	22,084 (44.0)	18,266 (36.3)	
> 85	36,257 (36.1)	14,128 (28.2)	22,129 (44.0)	
Sex No. (%)				<0.0001
Male	34,965 (34.8)	18,382 (36.6)	16,583 (32.9)	
Female	65,550 (65.2)	31,791 (63.4)	33,759 (67.1)	
Race No. (%)				<0.0001
White	87,281 (86.8)	43,287 (86.3)	43,994 (87.4)	
Black	5,891 (5.9)	2,872 (5.7)	3,019 (6.0)	
Asian	2,626 (2.6)	1,526 (3.0)	1,100 (2.2)	
Hispanic	2,884 (2.9)	1,556 (3.1)	1,328 (2.6)	
Other [c]	1,833 (1.8)	932 (1.9)	901 (1.8)	
Median income (median)	$49,987.00	$50,660.0	$49,443.0	<0.0001
Geographical Region No. (%)				<0.0001
Midwest	25,954 (25.8)	12,653 (25.2)	13,301 (26.4)	
Northeast	21,338 (21.2)	11,048 (22.0)	10,290 (20.4)	
South	37,701 (37.5)	18,671 (37.2)	19,030 (37.8)	
West	15,109 (15.0)	7,583 (15.1)	7,526 (15.0)	
Provider characteristics per 100,000 (median)				
Physicians	233.6	239.4	231	<0.0001
Hospitals	1.6	1.5	1.7	<0.0001
Hospitals with neurological services	0.6	0.6	0.6	0.1062
Hospitals with trauma services	0.2	0.2	0.2	0.0346
Hospital beds	301.9	301.6	304.1	<0.0001
Chronic Conditions No. (%)				
Hypertension	91,228 (90.8)	47,448 (94.6)	43,780 (87.0)	<0.0001
Hyperlipidemia	75,578 (75.2)	46,715 (93.1)	28,863 (57.3)	<0.0001
Ischemic heart disease	69,679 (69.3)	38,670 (77.1)	31,009 (61.6)	<0.0001
Congestive heart failure	51,346 (51.1)	26,949 (53.7)	24,397 (48.5)	<0.0001
Acute myocardial infarction	8,750 (8.7)	6,112 (12.2)	2,638 (5.2)	<0.0001
Valvular Heart Disease	8,893 (8.9)	5,041 (10.1)	3,852 (7.7)	<0.0001
Diabetes	42,851 (42.6)	25,663 (51.2)	17,188 (34.1)	<0.0001
ADRD	38,603 (38.4)	16,799 (33.5)	21,804 (43.3)	<0.0001
Comorbidity burden[d] mean (SD)	5.0 (2.3)	5.0 (2.3)	5.0 (2.3)	0.7705

Characteristics	Total Sample (n=100,515)	Statin Use [a]		P-value [b]
		Statin Users (n=50,173)	Non-Users (n=50,342)	
Prior stroke No. (%)	11,128 (11.1)	6,444 (12.8)	4,684 (9.3)	<0.0001
Prior ischemic stroke	10,197 (10.1)	5,986 (11.9)	4,211 (8.4)	<0.0001
Prior hemorrhagic stroke	1,334 (1.3)	680 (1.4)	654 (1.3)	0.4363
Injury severity				
Mean length of hospital stay (SD)	6.4 (8.1)	6.4 (8.5)	6.3 (7.6)	0.0043
Mean SRRI (SD)	0.90 (0.1)	0.90 (0.1)	0.90 (0.1)	0.7192

[a] Beneficiaries were categorized as non-users if they did not use statins at any time during study period, while beneficiaries were categorized as users if they had any statin use at any time during study period

[b] P-value from chi-square for categorical variables, Student's t-test for continuous variables and Wilcoxon signed rank sum test to test differences between medians reflects comparison between statin users and non-users

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

[d] Comorbidity burden: count of chronic conditions excluding cardiovascular conditions (hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, acute myocardial infarction, valvular heard disease) and diabetes and ADRD

Abbreviations: TBI, traumatic brain injury; SD, standard deviation; SNF, skilled nursing facility; ADRD, Alzheimer's disease and related dementias

Table 2

RRs (95% CIs) of mortality following TBI among Medicare beneficiaries, comparing post-TBI statin use to non-use

	Unadjusted			
	All mortality	**30-day mortality**	**60-day mortality**	**90-day mortality**
Any statin use	0.34 (0.33, 0.35)	0.09 (0.08, 0.11)	0.36 (0.32, 0.40)	0.38 (0.33, 0.43)
Atorvastatin	0.30 (0.28, 0.32)	0.08 (0.06, 0.11)	0.36 (0.29, 0.44)	0.36 (0.28, 0.46)
Fluvastatin	0.27 (0.18, 0.39)	0.07 (0.01, 0.49)	N/A [a]	0.19 (0.03, 1.33)
Lovastatin	0.28 (0.25, 0.32)	0.02 (0.01, 0.07)	0.27 (0.17, 0.44)	0.35 (0.22, 0.56)
Pravastatin	0.31 (0.28, 0.34)	0.11 (0.06, 0.18)	0.24 (0.14, 0.39)	0.32 (0.20, 0.51)
Rosuvastatin	0.22 (0.19, 0.25)	0.05 (0.02, 0.11)	0.18 (0.10, 0.33)	0.21 (0.11, 0.39)
Simvastatin	0.39 (0.38, 0.41)	0.11 (0.10, 0.14)	0.43 (0.37, 0.50)	0.44 (0.38, 0.52)
	Adjusted [b]			
	All mortality	**30-day mortality**	**60-day mortality**	**90-day mortality**
Any statin use	0.32 (0.31, 0.33)	0.16 (0.14, 0.19)	0.41 (0.35, 0.47)	0.40 (0.34, 0.47)
Atorvastatin	0.31 (0.29, 0.33)	0.16 (0.12, 0.21)	0.45 (0.36, 0.57)	0.44 (0.34, 0.56)
Fluvastatin	0.26 (0.18, 0.38)	0.14 (0.02, 0.96)	N/A [a]	0.20 (0.03, 1.44)
Lovastatin	0.29 (0.26, 0.33)	0.05 (0.01, 0.14)	0.34 (0.21, 0.57)	0.42 (0.26, 0.68)
Pravastatin	0.30 (0.27, 0.33)	0.19 (0.11, 0.32)	0.29 (0.17, 0.48)	0.35 (0.22, 0.56)
Rosuvastatin	0.25 (0.22, 0.29)	0.10 (0.05, 0.23)	0.25 (0.14, 0.48)	0.28 (0.15, 0.52)
Simvastatin	0.35 (0.34, 0.37)	0.18 (0.15, 0.22)	0.45 (0.37, 0.53)	0.73 (0.35, 0.52)

[a] N/A—estimate is too small and unreliable

[b] Adjusted for sociodemographic characteristics (age, race, sex, county-level income, LIS status, region); CVD (CHF, AMI, IHD, valvular heart disease, hyperlipidemia, hypertension); diabetes; ADRD; count of CCW chronic conditions excluding CVD and ADRD and diabetes; injury severity (LOS, discharge status, SRRi); medication use in month (anticoagulant use, antiplatelet use, beta-blocker); healthcare provider characteristics per 100,000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds); pre-TBI statin use

Table 3

RRs (95% CIs) of associated morbidities following TBI among Medicare beneficiaries, comparing post-TBI statin use to non-use

	Any Stroke	**Ischemic stroke**	**Hemorrhagic stroke**	**Depression**	**ADRD**
	Unadjusted				
Any statin use	1.00 (0.96, 1.04)	1.09 (1.04, 1.14)	0.81 (0.75, 0.87)	0.87 (0.83, 0.90)	0.76 (0.73, 0.79)
Atorvastatin	0.97 (0.91, 1.04)	1.04 (0.97, 1.12)	0.84 (0.74, 0.96)	0.81 (0.75, 0.88)	0.73 (0.69, 0.78)
Fluvastatin	0.87 (0.57, 1.33)	0.84 (0.52, 1.38)	0.77 (0.34, 1.71)	0.85 (0.56, 1.29)	0.78 (0.54, 1.11)
Lovastatin	0.91 (0.81, 1.04)	1.00 (0.87, 1.15)	0.72 (0.55, 0.93)	0.80 (0.70, 0.93)	0.76 (0.68, 0.85)
Pravastatin	1.06 (0.95, 1.18)	1.13 (1.00, 1.28)	0.75 (0.60, 0.95)	0.84 (0.74, 0.96)	0.68 (0.61, 0.76)
Rosuvastatin	1.00 (0.89, 1.14)	1.17 (1.02, 1.34)	0.67 (0.50, 0.88)	0.79 (0.68, 0.92)	0.62 (0.55, 0.70)
Simvastatin	1.02 (0.97, 1.07)	1.10 (1.04, 1.16)	0.85 (0.77, 0.94)	0.93 (0.88, 0.98)	0.83 (0.79, 0.87)
	Adjusted [a]				
Any statin use	0.86 (0.81, 0.91)	0.91 (0.85, 0.96)	0.75 (0.67, 0.83)	0.85 (0.79, 0.90)	0.77 (0.73, 0.81)
Atorvastatin	0.86 (0.80, 0.93)	0.90 (0.83, 0.98)	0.80 (0.69, 0.93)	0.81 (0.74, 0.89)	0.76 (0.71, 0.82)
Fluvastatin	0.81 (0.53, 1.25)	0.78 (0.48, 1.28)	0.71 (0.30, 1.72)	0.76 (0.48, 1.20)	0.76 (0.53, 1.08)
Lovastatin	0.84 (0.74, 0.97)	0.91 (0.79, 1.06)	0.70 (0.53, 0.92)	0.82 (0.71, 0.96)	0.81 (0.72, 0.92)
Pravastatin	0.91 (0.81, 1.02)	0.93 (0.82, 1.06)	0.71 (0.55, 0.91)	0.84 (0.73, 0.96)	0.69 (0.62, 0.77)
Rosuvastatin	0.88 (0.77, 1.00)	0.98 (0.85, 1.13)	0.67 (0.50, 0.90)	0.83 (0.71, 0.97)	0.68 (0.60, 0.78)
Simvastatin	0.86 (0.81, 0.91)	0.90 (0.84, 0.96)	0.78 (0.69, 0.88)	0.88 (0.82, 0.95)	0.83 (0.78, 0.88)

[a]All models adjusted for sociodemographic characteristics (age, race, sex, county-level income, LIS status, region); CVD (CHF, AMI, IHD, valvular heart disease, hyperlipidemia, hypertension); diabetes; ADRD; count of CCW chronic conditions excluding CVD and ADRD and diabetes; injury severity (LOS, discharge status, SRRi); healthcare provider characteristics per 100,000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds); pre-TBI statin use. Stroke models also included medication use in month (anticoagulant use, antiplatelet use, beta-blocker); history of either any stroke, ischemic stroke, or hemorrhagic stroke six months prior to TBI. Depression models also included beta-blocker use in month

Table 4

RR (95% CIs) of associated morbidities following TBI among Medicare beneficiaries, comparing statin use to non-use among beneficiaries with at least 12 months of observation time following TBI (n=74,386)

	Any Stroke	Ischemic stroke	Hemorrhagic stroke	Depression	ADRD
Unadjusted					
Any statin use	1.01 (0.96, 1.05)	1.09 (1.04, 1.14)	0.79 (0.72, 0.86)	0.88 (0.84, 0.92)	0.79 (0.76, 0.82)
Atorvastatin	0.97 (0.90, 1.04)	1.03 (0.95, 1.12)	0.82 (0.71, 0.95)	0.82 (0.76, 0.89)	0.77 (0.72, 0.82)
Fluvastatin	0.94 (0.60, 1.45)	0.90 (0.54, 1.49)	0.82 (0.34, 1.96)	0.90 (0.58, 1.37)	0.80 (0.55, 1.17)
Lovastatin	0.95 (0.83, 1.08)	1.01 (0.87, 1.17)	0.79 (0.60, 1.05)	0.81 (0.70, 0.94)	0.79 (0.70, 0.89)
Pravastatin	1.05 (0.93, 1.18)	1.12 (0.99, 1.27)	0.67 (0.51, 0.89)	0.86 (0.75, 0.98)	0.71 (0.64, 0.80)
Rosuvastatin	1.02 (0.89, 1.17)	1.18 (1.02, 1.35)	0.65 (0.48, 0.90)	0.81 (0.70, 0.95)	0.67 (0.59, 0.76)
Simvastatin	1.03 (0.98, 1.09)	1.11 (1.04, 1.17)	0.83 (0.74, 0.92)	0.94 (0.89, 1.00)	0.86 (0.82, 0.90)
Adjusted [a]					
Any statin use	0.84 (0.79, 0.89)	0.88 (0.83, 0.94)	0.72 (0.64, 0.81)	0.84 (0.79, 0.90)	0.79 (0.75, 0.83)
Atorvastatin	0.84 (0.77, 0.91)	0.87 (0.79, 0.95)	0.77 (0.64, 0.91)	0.81 (0.74, 0.89)	0.78 (0.72, 0.84)
Fluvastatin	0.84 (0.53, 1.31)	0.80 (0.48, 1.33)	0.71 (0.37, 1.91)	0.79 (0.49, 1.25)	0.76 (0.52, 1.11)
Lovastatin	0.85 (0.73, 0.98)	0.89 (0.76, 1.04)	0.75 (0.56, 1.01)	0.83 (0.71, 0.97)	0.83 (0.74, 0.95)
Pravastatin	0.88 (0.77, 0.99)	0.90 (0.79, 1.03)	0.62 (0.46, 0.84)	0.85 (0.73, 0.98)	0.71 (0.63, 0.80)
Rosuvastatin	0.86 (0.75, 0.99)	0.95 (0.82, 1.10)	0.64 (0.46, 0.89)	0.83 (0.71, 0.97)	0.72 (0.63, 0.82)
Simvastatin	0.84 (0.79, 0.90)	0.88 (0.82, 0.94)	0.75 (0.66, 0.86)	0.88 (0.82, 0.95)	0.85 (0.80, 0.90)

[a] All models adjusted for sociodemographic characteristics (age, race, sex, county-level income, LIS status, region); CVD (CHF, AMI, IHD, valvular heart disease, hyperlipidemia, hypertension); diabetes; ADRD; count of CCW chronic conditions excluding CVD and ADRD and diabetes; injury severity (LOS, discharge status, SRRi); healthcare provider characteristics per 100,000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds); pre-TBI statin use. Stroke models also included medication use in month (anticoagulant use, antiplatelet use, beta-blocker); history of either any stroke, ischemic stroke, or hemorrhagic stroke six months prior to TBI. Depression models also included beta-blocker use in month