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# Benefits and Risks of Anticoagulation Resumption Following Traumatic Brain Injury

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## Abstract

**IMPORTANCE—**The increased risk of hemorrhage associated with anticoagulant therapy following traumatic brain injury creates a serious dilemma for medical management of older patients: Should anticoagulant therapy be resumed after traumatic brain injury, and if so, when?

**OBJECTIVE—**To estimate the risk of thrombotic and hemorrhagic events associated with warfarin therapy resumption following traumatic brain injury.

**DESIGN, SETTING, AND PARTICIPANTS—**Retrospective analysis of administrative claims data for Medicare beneficiaries aged at least 65 years hospitalized for traumatic brain injury during 2006 through 2009 who received warfarin in the month prior to injury (n = 10 782).

**INTERVENTION—**Warfarin use in each 30-day period following discharge after hospitalization for traumatic brain injury.

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**Author Contributions:** Dr Albrecht had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Albrecht, Liu, Baumgarten, Rattinger, Smith, Gambert, Gottlieb, Zuckerman.

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*Study supervision:* Smith, Zuckerman.

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**MAIN OUTCOMES AND MEASURES—**The primary outcomes were hemorrhagic and thrombotic events following discharge after hospitalization for traumatic brain injury. Hemorrhagic events were defined on inpatient claims using International Classification of Diseases, Ninth Revision, Clinical Modification codes and included hemorrhagic stroke, upper gastrointestinal bleeding, adrenal hemorrhage, and other hemorrhage. Thrombotic events included ischemic stroke, pulmonary embolism, deep venous thrombosis, and myocardial infarction. A composite of hemorrhagic or ischemic stroke was a secondary outcome.

**RESULTS—**Medicare beneficiaries with traumatic brain injury were predominantly female (64%) and white (92%), with a mean (SD) age of 81.3 (7.3) years, and 82% had atrial fibrillation. Over the 12 months following hospital discharge, 55% received warfarin during 1 or more 30-day periods. We examined the lagged effect of warfarin use on outcomes in the following period. Warfarin use in the prior period was associated with decreased risk of thrombotic events (relative risk [RR], 0.77 [95% CI, 0.67-0.88]) and increased risk of hemorrhagic events (RR, 1.51 [95% CI, 1.29-1.78]). Warfarin use in the prior period was associated with decreased risk of hemorrhagic or ischemic stroke (RR, 0.83 [95% CI, 0.72-0.96]).

**CONCLUSIONS AND RELEVANCE—**Results from this study suggest that despite increased risk of hemorrhage, there is a net benefit for most patients receiving anticoagulation therapy, in terms of a reduction in risk of stroke, from warfarin therapy resumption following discharge after hospitalization for traumatic brain injury.

Traumatic brain injury (TBI) results in 142 000 emergency department visits, 81 500 hospitalizations, and 14 300 deaths annually among older adults.[1(p15)] Risk of venous thromboembolism (VTE) and stroke increases substantially following TBI.[2-6] Treatment with anticoagulant therapy can reduce the risk of thrombotic events after TBI, but this benefit must be balanced against the potential for a higher risk of bleeding, particularly intracranial hemorrhage.[2,7-9]

The situation in older adults is complicated by the presence of comorbid conditions such as atrial fibrillation that are indications for long-term anticoagulant therapy. The increased risk of hemorrhage associated with anticoagulant therapy following TBI creates a serious dilemma for medical management of older patients with TBI: should anticoagulant therapy be resumed after TBI, and if so, when?

Current clinical guidelines do not address the efficacy, safety, or timing of resumption of long-term anticoagulant therapy in older adults after traumatic events in general, or specifically after TBI.[10] This may be due to the lack of clinical trials or observational studies investigating this issue. Prior studies examining anticoagulant therapy to reduce risk of VTE in patients with TBI have focused on the period immediately after injury and have not provided conclusive results regarding prevention of VTE or risk of hemorrhage.[7,11-13] Studies assessing the impact of early (≤72 hours post-TBI) vs late (>72 hours post-TBI) initiation of anticoagulation therapy on risk of VTE or hemorrhage have also reported conflicting results.[14,15] These studies were limited by small sample size, but more importantly, none focused on risk of stroke. Furthermore, patients who had been receiving anticoagulation therapy prior to TBI often were excluded.

The purpose of this study was to estimate the risk of thrombotic and hemorrhagic events as a function of the timing of anticoagulant therapy resumption following TBI. This information will inform physician and patient decision making regarding optimal timing of anticoagulant resumption following TBI.

## Methods

### Study Sample

This study was approved by the institutional review board of the University of Maryland, Baltimore. The study met federal requirements to allow a waiver of informed consent. Medicare administrative data obtained from the Centers for Medicare & Medicaid Services (CMS) Chronic Condition Data Warehouse (CCW) were the primary sources of data for this study. We used the Centers for Disease Control and Prevention's case definition for TBI, which has been used in multiple publications and has been previously reported to have a sensitivity of 89% to detect severe TBI and a positive predictive value of 93%.[16-20] All Medicare beneficiaries with a discharge diagnosis of TBI (International Classification of Diseases, Ninth Revision, Clinical Modification [*ICD-9-CM*] codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, 950.1-950.3, 959.01) in any position on an inpatient claim between May 30, 2006, and December 31, 2009, and meeting inclusion criteria were included in the study. Inclusion criteria were as follows: age at least 65 years at the time of TBI, survival to hospital discharge, continuous enrollment in Medicare Parts A and B with no Part C enrollment for at least 6 months prior to the date of hospital admission for TBI, enrollment in Part D Prescription Drug Plan during the month before TBI and during all follow-up time after TBI, receipt of warfarin sodium in the month preceding TBI, and no TBI episode in the 6 months prior to the index TBI event. New claims for TBI occurring within 14 days of a previous TBI discharge were combined to form a single hospitalization episode with an admission date reflecting the earliest TBI claim's admission date and a discharge date reflecting the latest TBI claim's discharge date.

### Exposure

The primary exposure was warfarin use after TBI, but we also analyzed use of other anticoagulants. We searched for all anticoagulant medications in the Part D prescription drug events file and in the Part B administrative claims (because some of these medications are injectable). We created 2 groups of anticoagulants: warfarin and other anticoagulants. The other anticoagulants included platelet-reducing agents, platelet aggregation inhibitors, and thrombolytic agents. We divided follow-up time after discharge from TBI hospitalization into 30-day periods and recorded filled prescriptions and proportion of days covered (number of daily doses in the prescription/number of days in the period) for all anticoagulants in each 30-day period with Part D coverage. Some prescriptions are written for 90 rather than 30 days. Therefore, it was possible for a beneficiary to have no prescriptions filled during a period but still have a proportion of days covered by that prescription greater than 0. Warfarin use during each 30-day period was defined as either a filled prescription for an anticoagulant or a proportion of days covered by an anticoagulant greater than 0. Warfarin use could begin at any time during the 30-day period, including before or after the outcome event of interest. Because we were interested in the causal effect

of warfarin use on our outcomes, we lagged it by 1 month such that risk of an outcome in a given period was modeled on the basis of warfarin use in the previous period. Part D does not consistently include prescriptions filled during skilled nursing facility (SNF) stays because they are covered as part of the SNF payment. Therefore, patients discharged to an SNF had missing values for warfarin use during the SNF stay. Use of other anticoagulants was defined similarly.

## Outcomes

The primary outcomes of interest were hemorrhagic and thrombotic events following discharge from hospitalization for TBI. Hemorrhagic and thrombotic events occurring during the TBI hospitalization may appear in claims data as separate hospitalizations. To ensure that we were capturing only new events after TBI, we required that there be an interval of at least 2 weeks between discharge from the index TBI hospitalization and a subsequent hospitalization for a hemorrhagic or thrombotic event.

A hemorrhagic event was defined as the presence of any of the following *ICD-9-CM* codes in any position on an inpatient claim: hemorrhagic stroke (430.xx-432.xx), upper gastrointestinal bleeding (531.xx, 532.xx, 533.xx, 534.xx, 578.xx), adrenal hemorrhage (772.5x), and other hemorrhage (568.81, 719.1x, 423.0x, 455.2x, 455.5x, 456.0x, 456.20, 455.8x, 459.0x, 530.21, 530.7x, 535.x1, 537.83, 562.12, 562.13, 569.3x, 569.85, 578.0x, 578.1x, 578.9x, 596.7x, 599.7x, 782.7x, 784.7x, 786.3x, 853.xx). Thrombotic events included ischemic stroke (433.xx, 434.xx, 435.xx, 437.0x, 437.1x), pulmonary embolism (415.1x), deep venous thrombosis (451.1x, 451.2x, 451.81, 451.9x, 453.4x), and myocardial infarction (410.xx). These *ICD-9-CM* codes have been used previously to identify major hemorrhagic and thrombotic events and reported to have positive predictive values of greater than 85%.[21-24] A composite of hemorrhagic or ischemic stroke was a secondary outcome.

## Covariates

Demographic characteristics were obtained from the CCW file. Baseline comorbidities at TBI hospitalization were determined using CMS's CCW 27 flagged comorbid conditions.[25] These chronic conditions are identified on the basis of the presence of *ICD-9-CM* codes on inpatient, SNF, home health, or outpatient claims using algorithms defined by CMS. If the date of first diagnosis of a particular chronic condition was prior to the date of TBI hospitalization, the patient was considered to have that chronic condition at baseline. We also created the following indicator variables by searching *ICD-9-CM* diagnosis codes from any claim during the study period, using the date of first diagnosis to determine whether the condition was present at baseline: atrial flutter (427.32), valvular heart disease (394.x-397.x, 398.9x, V42.2, V43.3), chronic liver disease (571.2x, 571.5x, 571.6x, 070.0x, 070.2x, 070.4x, 070.6x, 070.71, 348.3x, 456.00-456.2x, 572.20-572.4x, 782.4x, 789.59, 155.x, V42.7, 50.5, 471.35, 471.36), coagulation defect (286.x, 287.x), hypercoagulopathy (289.8), or neurological disease (332.x, 340.x, 342.x-344.x, 436.x). We created indicator variables for hemorrhagic and thrombotic events occurring prior to TBI using methods similar to those described for outcome events. For descriptive purposes, we created risk scores based on previously reported clinical classification schemes predicting stroke risk ($CHADS_2$

[congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack]) and hemorrhage risk ($HEMORR_2HAGES$ [hepatic or renal disease, ethanol abuse, malignant neoplasm, older age (>75), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors (*CYP2C9* variant), excessive fall risk, stroke]) in patients with atrial fibrillation.[26,27] We modified the $HEMORR_2HAGES$ score to accommodate variables available in our data. The modified score included the following: previous hemorrhagic event, liver disease, chronic kidney disease, ethanol abuse, malignant neoplasm, hypertension, anemia, coagulation defect, and neurological disease. We dichotomized the $CHADS_2$ score (≤2, >2) and the modified $HEMORR_2HAGES$ score (≤3, >3). Length of TBI hospital stay was classified into 4 categories: 0 to 2, 3 to 5, 6 to 8, and 9 or more days.

Beneficiaries may have developed comorbid conditions during the follow-up period that could have affected warfarin use or risk of outcomes. Therefore, using the date of first diagnosis of new-onset comorbid conditions, we created time-varying indicator variables for the CCW's 27 comorbid conditions and the comorbidity variables that we created, and we incorporated these into our models to adjust for potential confounding.

## Data Analysis

We created a categorical variable representing months of warfarin use during the 12 months following hospital discharge for TBI (no warfarin use, 1-6 months warfarin use, 7-12 months warfarin use) and examined the associations of warfarin use and outcome (hemorrhagic or thrombotic events) variables with demographic characteristics and baseline comorbidities using $\chi^2$ tests for dichotomous covariates, *t* tests, Wilcoxon rank sum tests, or analysis of variance as appropriate to assess potential confounding.

Beneficiaries contributed follow-up time to our study if they were enrolled in Medicare Parts A and B, with no Part C enrollment, at any time between May 31, 2006, and December 31, 2009. Once entered into the cohort, beneficiaries continued to contribute follow-up time until December 31, 2009, unless they (1) were deceased or (2) enrolled in a Medicare Advantage (Part C) plan. We computed the unadjusted incidence rate of each outcome by counting person-months after TBI while using warfarin and person-months while not using warfarin. These numbers were divided into the number of outcome events. Annualized rates per 1000 beneficiaries and 95% confidence intervals (CIs) are reported separately for beneficiaries using and not using warfarin. We also calculated rate differences and 95% CIs for each event between those using and not using warfarin.

We used a discrete time approach to model risk of the primary outcomes as a function of lagged warfarin use and covariates per 30-day period following discharge from TBI hospitalization and limited our analysis to the first 12 periods following hospital discharge to avoid sample size problems due to censoring. To accomplish this, we used generalized linear models with a binomial distribution and a complementary log-log link.[28(pp211-231)] We examined time (period) as continuous and categorical and used the log likelihood scores to choose the best-fitting model. We created 2 early (within 3 months following hospital discharge for TBI, and within 6 months) vs late (>3 months following hospital discharge for TBI, and >6 months) warfarin use resumption variables. We examined interactions between

the lagged warfarin use variable and period, “early” resumption, discharge to SNF, stroke risk ($CHADS_2$, >2), and hemorrhagic risk (modified $HEMORR_2HAGES$, >3). As a secondary analysis, we modeled each individual outcome as a function of lagged warfarin use and covariates.

The final model for hemorrhagic outcomes included the following time-invariant and time-varying variables: age, sex, race, pre-TBI hemorrhagic event, lagged warfarin use, period (continuous), other anticoagulant use in the period, length of hospital stay (categorical), discharge to SNF, atrial fibrillation, liver disease, chronic kidney disease, ethanol abuse, malignant neoplasm, hypertension, anemia, coagulation defect, neurological disease, and thrombotic event in the period. The final model for thrombotic outcomes included the following time-invariant and time-varying variables: age, sex, race, pre-TBI thrombotic event, lagged warfarin use, hemorrhagic event in the period, period (continuous), other anticoagulant use in the period, length of hospital stay (categorical), discharge to SNF, stroke or transient ischemic attack, hypertension, diabetes mellitus, and heart failure. The model for the composite outcome of hemorrhagic or ischemic stroke contained all covariates included in the individual models. As a sensitivity analysis, we created a cohort of patients with atrial fibrillation who met all inclusion criteria and performed the analyses described above. To determine whether missing warfarin use information due to SNF stays was biasing our estimates, we performed additional sensitivity analyses. We restricted to periods 4 through 12 when the majority of beneficiaries had been discharged from an SNF. We also artificially assigned all beneficiaries in an SNF to warfarin use and then to no warfarin use and tested the effect on our estimates.

In an observational study, bias can be introduced because participants are not randomized to treatment. As a sensitivity analysis, we created inverse probability of treatment weights (IPTWs) to adjust for potential selection bias introduced by the observational study design.[29] To generate IPTWs, receipt of warfarin in each 30-day period following hospital discharge for TBI was modeled as a function of risk factors for hemorrhagic and thrombotic outcomes (2 separate models). We normalized the IPTWs prior to inclusion in the final models.

Statistical significance was defined as $P < .05$. All analyses were performed with SAS software, version 9.2.

## Results

There were 115 334 beneficiaries with TBI who had at least 6 months of Medicare Parts A and B with no Part C coverage prior to TBI. Of these, 9902 (9%) died during TBI hospitalization. Of the remaining beneficiaries (n = 105 432), 14 936 (14%) were prescribed warfarin in the month before TBI and 10 782 (72% of those prescribed warfarin in the month prior to TBI) did not have a hemorrhagic or thrombotic event during hospitalization for TBI. This group formed our study sample.

Mean (SD) age was 81.3 (7.3) years (**Table 1**). The sample was predominantly female (64%) and white (92%), with a high prevalence of comorbidity. The most common

comorbidities were hypertension (96%), ischemic heart disease (85%), atrial fibrillation (82%), and heart failure (75%). Among the 1939 of 10 782 (18%) without atrial fibrillation, 1409 of 10 782 (13%) had ischemic heart disease, 32 (0.3%) had valvular heart disease, and 215 (2%) had a prior thrombotic event as indications for warfarin therapy. Forty percent were discharged to an SNF. Mean (SD) length of follow-up after discharge from hospitalization for TBI was 594.9 (405.6) days.

Twenty-six percent of beneficiaries received warfarin in the first period following discharge from TBI hospitalization, and 28% had missing anticoagulation information due to an SNF stay (**Table 2**). In postdischarge period 3, 44% of beneficiaries received warfarin and only 12% had missing information. From periods 6 to 24, the percentage of beneficiaries using warfarin declined from 48% to 44%, and the percentage of beneficiaries with missing warfarin use information remained steady at 7%. Following discharge from hospitalization for TBI, 4983 beneficiaries (46%) had used warfarin during at least 1 period by 3 months, 5721 (53%) had used warfarin during at least 1 period by 6 months, and 5971 (55%) had used warfarin during at least 1 period by 12 months. At the same time, use of other anticoagulants increased slightly (from 7% in period 1 to 8% in period 12).

Beneficiaries differed by warfarin use categories (Table 1). Beneficiaries who used warfarin for 7 to 12 months (mean [SD] age, 80.1 [7.2] years) were younger than those who used warfarin for 1 to 6 months (mean [SD] age, 81.0 [7.4] years) and those who did not use warfarin (mean [SD] age, 82.4 [7.3] years; analysis of variance $P < .001$). They were less likely to have a hospital stay of 9 or more days (15% vs 17% vs 28%; $P < .001$). Beneficiaries who used warfarin for 7 to 12 months were less likely to have Alzheimer disease and related dementias (27% vs 35% vs 39%; $P < .001$).

There were 962 thrombotic events and 731 hemorrhagic events during the 12 months following hospital discharge for TBI (**Table 3**). There were 833 hemorrhagic or ischemic stroke events. No adrenal hemorrhage events were recorded. During the 12 months following TBI, the unadjusted annualized rate of thrombotic events per 1000 beneficiaries was 113.5 (95% CI, 102.9-125.2) among those using warfarin and 155.9 (95% CI, 143.5-169.3) among those not using warfarin (Table 3). The rate of hemorrhagic events per 1000 beneficiaries was 119.8 (95% CI, 108.9-131.8) among those using warfarin and 85.7 (95% CI, 76.7-95.8) among those not using warfarin. The absolute rate difference of thrombotic events between beneficiaries using warfarin and beneficiaries not using warfarin was 42.4 (95% CI, 42.2-42.5), whereas the absolute rate difference of hemorrhagic events was 34.1 (95% CI, 33.9-34.2).

In the adjusted regression models, warfarin use in a given period reduced the risk of thrombotic events in the following period (relative risk [RR], 0.77 [95% CI, 0.67-0.88]) (Table 3). Warfarin use increased the risk of hemorrhagic events in the following period (RR, 1.51 [95% CI, 1.29-1.78]). Warfarin use reduced the risk of the composite outcome of hemorrhagic or ischemic stroke (RR, 0.83 [95% CI, 0.72-0.96]) in the following period. The interaction between period and lagged warfarin use was not statistically significant; therefore, the regression results are interpreted as the effect of the lagged warfarin use variable on outcomes averaged over the first 12 periods following discharge from

hospitalization for TBI. No other interactions with lagged warfarin use were statistically significant.

Restricting our analyses to patients with atrial fibrillation did not significantly affect estimates of the effect of warfarin receipt. The average SNF stay was right-skewed, with a mean of 62 days and a median of 32 days; therefore, restricting our analysis to periods 4 through 12 eliminated the majority of missing warfarin exposure information due to SNF stay but did not significantly affect our RR estimates. Artificially assigning all beneficiaries in an SNF to warfarin use and then to no warfarin use also had little effect on our estimates. Finally, we used IPTWs to eliminate possible confounding by indication, but these weights did not significantly change our RR estimates.

## Discussion

In this national cohort of Medicare beneficiaries who were receiving warfarin prior to TBI, 55% used warfarin at least once during the year following TBI. Warfarin use after TBI was associated with reduced risk of thrombosis and increased risk of hemorrhagic events. Importantly, warfarin use after TBI was associated with reduced risk of ischemic and hemorrhagic stroke.

The benefits of anticoagulation therapy to reduce stroke risk in patients with atrial fibrillation are well established.[30,31] Nonetheless, anticoagulation therapy is underutilized, with reported prevalence of anticoagulation therapy ranging from 31% to 56% among patients with atrial fibrillation[32-34] In our study, all participants received warfarin in the month prior to TBI and 82% had atrial fibrillation, yet only 55% of participants resumed warfarin use for at least 1 month in the year following TBI.

Previous studies suggest that physician perceptions of the risks rather than the benefits associated with warfarin use drive the decision to prescribe warfarin.[35,36] The most often cited barriers to warfarin prescription are a history of bleeding, fall risk, cognitive impairment, and advanced age.[35] Consistent with this, we observed that older patients and those with Alzheimer disease were less likely to receive warfarin following TBI. Patients who did not receive warfarin in the year following injury also had a longer hospital stay for TBI and were more likely to be discharged to an SNF, implying more severe injury that may have been perceived as a contraindication to resumption of warfarin therapy.

We observed an elevated risk of hemorrhagic events associated with warfarin use after TBI but a decreased risk of hemorrhagic stroke and thrombotic events. These effects did not change significantly over time, suggesting that barring strong contraindication, most patients would benefit, in terms of a reduction in the risk of stroke, from resuming warfarin therapy immediately following hospital discharge for TBI. These results are consistent with prior research conducted among patients with atrial fibrillation, suggesting that the benefits of warfarin use outweigh the risks, even among patients at high risk for falls.[32-38] Similarly, among patients who experienced an episode of warfarin-associated gastrointestinal tract bleeding, resumption of warfarin therapy has been found to decrease risk of thrombosis and death.[39]

Our observation that resumption of warfarin therapy following TBI was associated with a decreased risk of hemorrhagic stroke was likely due to residual confounding by indication, even though we controlled for comorbid conditions associated with increased risk of hemorrhage and used IPTWs to reduce selection bias. Uncontrolled hypertension, a major risk factor for hemorrhagic stroke, may have been an important but unmeasured potential confounder. Nonetheless, resumption of warfarin therapy following TBI was not associated with an increased risk of hemorrhagic stroke.

There are some limitations to consider when interpreting these results. Administrative data are designed for reimbursement; hence, certain fields may be incomplete, absent, or misleading. For example, our data did not capture TBI severity, which could strongly affect risk of hemorrhage and death. However, we were able to adjust our models for length of hospital stay and discharge to an SNF, variables that may be proxies for TBI severity. Ascertainment of medication use is based on filled prescriptions and proportion of days covered but does not provide information on medications left over from the pre-TBI period or adherence during the time covered by the fill, which could have resulted in misclassification of warfarin use. Second, our data captured diagnosis of hypertension, but as previously mentioned, we do not know whether the hypertension was controlled. Patients with more severe injury were more likely to be discharged to an SNF, resulting in missing warfarin exposure information. It is possible that among these patients, warfarin therapy could have a different effect on risk of hemorrhagic or thrombotic events. Nonetheless, our sensitivity analyses suggest that the missing information had little effect on our RR estimates. Although we were able to control for other anticoagulant use, some patients may have been taking aspirin, which is not captured in Part D claims.

## Conclusions

This large, national study documents warfarin treatment patterns and reports for the first time, to our knowledge, on the benefits and risks of warfarin use following discharge from hospitalization for TBI. Results from this study suggest that despite increased risk of hemorrhage, there is a benefit for most patients receiving anticoagulation therapy, in terms of a reduction in risk of stroke, from warfarin therapy resumption following discharge after hospitalization for TBI. This study quantifies the risks and benefits associated with resumption of warfarin therapy following TBI and provides objective information that will help patients and clinicians make informed treatment decisions.

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## Table 1

Characteristics of Medicare Beneficiaries Who Used Warfarinin the Month Prior to Traumatic Brain Injury (TBI),by Warfarin Use During the Year Following Hospital Discharge

| Characteristic | Total Sample (N = 10 782) | Warfarin Use[a] | | | *P* Value[b] |
|---|---|---|---|---|---|
| | | None (n = 4971) | 1-6 mo (n = 1877) | 7-12 mo (n = 3934) | |
| Age, mean (SD), y | 81.3 (7.3) | 82.4 (7.3) | 81.0 (7.4) | 80.1 (7.2) | <.001 |
| Sex, No. (%) | | | | | |
| Female | 6932 (64) | 3315 (63) | 1186 (63) | 2611 (66) | .003 |
| Male | 3850 (36) | 1836 (37) | 691 (37) | 1323 (34) | |
| Race, No. (%) | | | | | |
| White | 9964 (92) | 4571 (92) | 1734 (92) | 3659 (93) | .31 |
| Black | 375 (3) | 191 (4) | 65 (4) | 119 (3) | |
| Other | 443 (4) | 209 (4) | 78 (4) | 156 (4) | |
| Comorbid disease at TBI hospitalization, No. (%) | | | | | |
| ADRD | 3663 (34) | 1948 (39) | 655 (35) | 1060 (27) | <.001 |
| Acute myocardial infarction | 1266 (12) | 625 (13) | 242 (13) | 399 (10) | .001 |
| Anemia | 8319 (77) | 3903 (79) | 1490 (79) | 2926 (74) | <.001 |
| Atrial fibrillation | 8843 (82) | 3978 (80) | 1532 (82) | 3333 (85) | <.001 |
| Heart failure | 8115 (75) | 3709 (75) | 1487 (79) | 2920 (74) | <.001 |
| Chronic kidney disease | 4085 (38) | 1952 (39) | 765 (41) | 1368 (35) | <.001 |
| Chronic obstructive pulmonary disease | 5020 (47) | 2231 (45) | 957 (51) | 1832 (47) | <.001 |
| Hypertension | 10 345 (96) | 4780 (96) | 1796 (96) | 3769 (96) | .58 |
| Ischemic heart disease | 9142 (85) | 4175 (84) | 1642 (87) | 3325 (85) | .001 |
| Malignant neoplasm | 2240 (21) | 1067 (21) | 388 (21) | 785 (20) | .22 |
| Valvular heart disease | 2172 (20) | 881 (18) | 422 (22) | 869 (22) | <.001 |
| Length of stay, No. (%), d | | | | | |
| 0-2 | 2596 (24) | 791 (16) | 538 (29) | 1267 (32) | <.001 |
| 3-5 | 4150 (38) | 1837 (37) | 734 (39) | 1579 (40) | |
| 6-8 | 1728 (16) | 927 (19) | 289 (15) | 512 (13) | |

| Characteristic | Total Sample (N = 10 782) | Warfarin Use[a] None (n = 4971) | 1-6 mo (n = 1877) | 7-12 mo (n = 3934) | *P* Value[b] |
|---|---|---|---|---|---|
| ≥9 | 2308 (21) | 1416 (28) | 316 (17) | 576 (15) | |
| Follow-up after TBI, mean (SD), d | 594.9 (405.6) | 482.2 (423.7) | 515.9 (385.5) | 775.1 (318.7) | <.001 |
| Discharge to SNF, No. (%) | 4282 (40) | 2358 (47) | 719 (38) | 1205 (31) | <.001 |
| $CHADS_2$ score >2, No. (%) | 8997 (83) | 4223 (85) | 1577 (84) | 3197 (81) | <.001 |
| Modified $HEMORR_2HAGES$ score >3, No. (%) | 6228 (58) | 2994 (60) | 1141 (61) | 2093 (53) | <.001 |
| Previous event, No. (%) | | | | | |
| Hemorrhagic | 1936 (18) | 969 (19) | 350 (19) | 617 (16) | <.001 |
| Thrombotic | 3083 (29) | 1498 (30) | 580 (31) | 1005 (26) | <.001 |

Abbreviations: ADRD, Alzheimer disease and related dementias; $CHADS_2$, congestive heart failure, hypertension, age≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; SNF, skilled nursing facility.

[a] Percentages may not total 100% because of rounding.

[b] $X^2$ Or analysis of variance *P* value represents comparison between warfarin use resumption groups.

## Table 2

Warfarin Use After Traumatic Brain Injury (TBI) Among Medicare Beneficiaries Who Used Warfarin in the Month Prior to TBI

| 30-Day Period After TBI Discharge | Total Sample | No. (%)[a] | | |
|---|---|---|---|---|
| | | Warfarin Use | No Warfarin Use | Missing Information |
| 1 | 10 782 | 2788 (26) | 5003 (46) | 2991 (28) |
| 3 | 9405 | 4108 (44) | 4121 (44) | 1176 (12) |
| 6 | 8677 | 4136 (48) | 3968 (46) | 573 (7) |
| 12 | 7713 | 3613 (47) | 3646 (47) | 454 (6) |
| 18 | 5693 | 2576 (45) | 2745 (48) | 372 (7) |
| 24 | 4050 | 1782 (44) | 2001 (49) | 267 (7) |

[a]Percentages may not total 100% because of rounding.

## Table 3

Frequencies, Unadjusted Annualized Incidence Rates of Outcomes per 1000 Beneficiaries, and Adjusted Relative Risk (RR) of the Association Between Warfarin Use in the Prior Period and Outcomes

| | During Warfarin Use | | Without Warfarin Use | | |
|---|---|---|---|---|---|
| Event | Events, No.[a] | Incidence Rate (95% CI) | Events, No.[a] | Incidence Rate (95% CI) | Adjusted RR (95% CI)[b] |
| Any thrombotic event | 400 | 113.5 (102.9-125.2) | 562 | 155.9 (143.5-169.3) | 0.77 (0.67-0.88) |
| Any ischemic stroke | 293 | 83.2 (75.4-91.7) | 453 | 125.7 (115.7-136.5) | 0.81 (0.69-0.95) |
| Pulmonary embolism | 28 | 7.9 (7.2-8.8) | 102 | 28.3 (26.0-30.7) | 0.35 (0.22-0.55) |
| Myocardial infarction | 115 | 32.6 (29.6-36.0) | 164 | 45.5 (41.9-49.4) | 0.87 (0.67-1.13) |
| Deep venous thrombosis | 91 | 25.8 (23.4-28.5) | 197 | 54.6 (50.3-59.4) | 0.63 (0.48-0.83) |
| Any hemorrhagic event | 422 | 119.8 (108.9-131.8) | 309 | 85.7 (76.7-95.8) | 1.51 (1.29-1.78) |
| Any hemorrhagic stroke | 75 | 21.3 (19.3-23.4) | 130 | 36.1 (32.3-40.3) | 0.70 (0.52-0.95) |
| Any upper gastrointestinal bleeding | 244 | 69.3 (62.9-76.2) | 154 | 42.7 (38.2-47.8) | 1.91 (1.54-2.38) |
| Any other hemorrhage | 384 | 109.0 (99.1-119.9) | 208 | 57.7 (51.6-64.5) | 2.31 (1.89-2.81) |
| Hemorrhagic or ischemic stroke | 339 | 96.2 (87.5-105.8) | 494 | 137.0 (122.6-153.2) | 0.83 (0.72-0.96) |

Abbreviation: TBI, traumatic brain injury.

[a] Columns may not add up as a result of exclusion of events occurring during hospitalization for TBI and multiple simultaneous events.

[b] All models were adjusted for age, sex, race, lagged warfarin use, 30-day period after TBI (continuous), other anticoagulant use in the 30-day period after TBI, length of hospital stay (categorical), and discharge to skilled nursing facility. In addition, the hemorrhagic models were adjusted for atrial fibrillation, liver disease, chronic kidney disease, ethanol abuse, malignant neoplasm, hypertension, anemia, coagulation defect, neurological disease, pre-TBI hemorrhagic event, and thrombotic event during period. The thrombotic models were adjusted for stroke or transient ischemic attack, hypertension, diabetes mellitus, heart failure, pre-TBI thrombotic event, and hemorrhagic event during period. The composite outcome model included all covariates from individual models except hemorrhagic or thrombotic event during period.