



CLINICAL RESEARCH STUDY

Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall

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ABSTRACT

PURPOSE: Patients at high risk for falls are presumed to be at increased risk for intracranial hemorrhage, and high risk for falls is cited as a contraindication to antithrombotic therapy. Data substantiating this concern are lacking.

METHODS: Quality improvement organizations identified 1245 Medicare beneficiaries who were documented in the medical record to be at high risk of falls and 18 261 other patients with atrial fibrillation. The patients were elderly (mean 80 years), and 48% were prescribed warfarin at hospital discharge. The primary endpoint was subsequent hospitalization for an intracranial hemorrhage, based on ICD-9 codes.

RESULTS: Rates (95% confidence interval [CI]) of intracranial hemorrhage per 100 patient-years were 2.8 (1.9–4.1) in patients at high risk for falls and 1.1 (1.0–1.3) in other patients. Rates (95% CI) of traumatic intracranial hemorrhage were 2.0 (1.3–3.1) in patients at high risk for falls and 0.34 (0.27–0.45) in other patients. Hazard ratios (95% CI) of other independent risk factors for intracranial hemorrhage were 1.4 (1.0–3.1) for neuropsychiatric disease, 2.1 (1.6–2.7) for prior stroke, and 1.9 (1.4–2.4) for prior major bleeding. Warfarin prescription was associated with intracranial hemorrhage mortality but not with intracranial hemorrhage occurrence. Ischemic stroke rates per 100 patient-years were 13.7 in patients at high risk for falls and 6.9 in other patients. Warfarin prescription in patients prone to fall who had atrial fibrillation and multiple additional stroke risk factors appeared to protect against a composite endpoint of stroke, intracranial hemorrhage, myocardial infarction, and death.

CONCLUSION: Patients at high risk for falls with atrial fibrillation are at substantially increased risk of intracranial hemorrhage, especially traumatic intracranial hemorrhage. However, because of their high stroke rate, they appear to benefit from anticoagulant therapy if they have multiple stroke risk factors.

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In atrial fibrillation trials of carefully selected participants, antithrombotic therapy prevented strokes with an acceptable rate of intracranial hemorrhages: 0.3 intracranial hemorrhage per 100 patient-years with aspirin and 0.4–0.5 intracranial hemorrhage per 100 patient-years with warfarin.^{1–3} However, elderly patients at high risk for falls were excluded from clinical trials,^{2–10} and no longitudinal data quantify the risk of intracranial hemorrhage and stroke in such patients.

Perception of traumatic intracranial hemorrhage risk influences selection of antithrombotic therapy. Surveys^{11,12} and medical record review¹³ demonstrate that physicians avoid antithrombotic therapy in elderly patients with atrial fibrillation who seem likely to fall and sustain an intracranial hemorrhage. Epidemiological studies have found that antithrombotic therapy can double the risk of intracranial hemorrhage,^{14,15} especially fatal events.¹⁶ Thus, accurate knowledge of the rate of intracranial hemorrhage in patients at high risk for falls with atrial fibrillation would help determine the optimal antithrombotic therapy.

Our primary goal was to quantify the incidence of intracranial hemorrhage in Medicare beneficiaries with atrial fibrillation who were at high risk of falls. Our secondary goals were to identify independent risk factors for intracranial hemorrhage and to quantify the benefits of warfarin therapy, if any, in patients at high risk for falls.

Methods

The primary endpoint was hospitalization for an intracranial hemorrhage after the index hospital admission. The study was approved by the Washington University human subjects' committee.

Formation of the second national registry of atrial fibrillation

The National Registry of Atrial Fibrillation II dataset was created from 23 657 anonymous patient records gathered by Quality Improvement Organizations for the National Stroke Project. The project was managed by the Iowa Foundation for Medical Care. The dataset included both Medicare records and chart-abstracted data from 3586 hospitals in all 50 US states. Medical records were selected as

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a random sample stratified by state from all Medicare beneficiaries who were hospitalized with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) code for atrial fibrillation (427.31) in any diagnostic position and who were discharged between April 1, 1998 and March 31, 1999. We obtained inpatient (part A) and outpatient (part B) Medicare records from 1995 through 1999.

The structured abstraction of data from medical charts was performed by the Clinical Data Abstraction Centers, which confirmed the presence of atrial fibrillation during the index admission. The remaining records were systematically reviewed for risk of falls, stroke risk factors, and discharge medications. Chart abstractors were unaware of the study's endpoints.

Outcomes assessment

Intracranial hemorrhage and ischemic strokes in the follow-up period were identified by recently validated ICD-9 codes in Medicare Part A data. We identified ischemic stroke from ICD-9 codes 433.x1, 434.x1, 436, 437.1, and 437.9 ("x" represents any digit) in any position. As compared to structured chart abstraction, these codes have a positive predictive value of 96%.¹⁷ We identified nontraumatic intracranial hemorrhages from codes 430x–432x and traumatic intracranial hemorrhage from codes 800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x, 803.7x, 803.7x, 804.2x, 804.3x, 804.7x, 804.8x, 852, and 853. The positive predictive value of these ICD-9 codes for intracranial hemorrhage is 77%.¹⁷

In a subgroup analysis we identified myocardial infarction from ICD-9 code 410.x and noncerebral hemorrhage based on ICD-9 codes validated by White et al.¹⁴ We assessed predictive validity of the high-fall-risk designation using Medicare Part A and B claims by assessing for falls (E880.0–E886.9, E888) and fractures (800–829).

In the primary analysis we censored patients at the time of their last hospitalization if they died outside of the hospital because neither Medicare Part A or B claims nor the Medicare Denominator File provides cause of death. Likewise, those who died after the baseline hospitalization (before another hospitalization) were excluded ($n = 1824$). In a secondary analysis, we included out-of-hospital deaths as part of a composite endpoint that also included stroke, intracranial hemorrhage, and myocardial infarction. For beneficiaries who experienced multiple adverse events, we excluded events and days of follow-up that occurred after the initial event.

Cohort formation

The only acceptable source of information for risk of falls was physician documentation in the medical record. The terms "frequent falls," "history of falls," "multiple falls," or "tendency for falls" were considered synonymous

with high risk for falls; a single fall was insufficient documentation for this designation. We also identified a trial-like cohort comprising patients who lacked the following comorbid conditions: high risk for falls, age 80 or older, chronic renal disease, uncontrolled hypertension, malignancy, alcoholism, history of bleeding, neuropsychiatric impairment, prior ischemic stroke or transient ischemic attack (TIA), anemia, bleeding disorder, and combination therapy with warfarin and aspirin at discharge.

Statistical analyses

We used time-to-event analyses to test our hypotheses that the risks of intracranial hemorrhage and of stroke were greater in patients at high risk for falls. We used backward elimination to develop parsimonious Cox models. We verified the proportionality assumption graphically and by time-dependent covariates. In the intracranial hemorrhage model, we tested for effects of history of ischemic stroke or TIA, age, sex, race, alcoholism, history of bleeding, a bleeding disorder (eg, hemophilia or leukemia), nursing home residence, neuropsychiatric impairment (schizophrenia, dementia, or Parkinson's disease), and antithrombotic therapy. In the ischemic stroke Cox model, we tested for effects of sex, nursing home residence, antithrombotic therapy, and stroke factors. We quantified the risk of stroke using a clinical prediction (CHADS₂) that assigns 1 point for the presence of Congestive heart failure, Hypertension, Age > 75, or Diabetes mellitus, and 2 points for a prior Stroke or TIA.^{18,19} In a subgroup analysis, we initially stratified the analysis into CHADS₂ scores of 0–1, 2, or 3–6, because the benefit of warfarin therapy is greater in patients with atrial fibrillation at greater risk of stroke.²⁰ Because the apparent benefit of warfarin was similar in patients with 2 points and with 3–6 points, we combined these two cohorts.

Statistical tests were two-tailed. We performed statistical analyses in SAS version 9.0 (SAS Institute Inc; Cary, NC).

Results

Cohort descriptions

Subjects at high risk for falls were older and had more comorbidities than other patients. In addition, they were significantly less likely to receive warfarin or aspirin therapy (Table 1).

Trial-like patients (n = 3236) were younger (mean age, 73 years) and healthier (mean number of bleeding risk factors, 0.6). Most of them were prescribed antithrombotic therapy (53.7% warfarin; 23.1% aspirin).

Data integrity and validation

We validated the fall-risk designation by examining ICD-9 codes for falling and for nonpathologic fractures that

Table 1 Demographic and clinical factors of study cohorts

Variable	High-fall-risk patients n = 1245	Other patients n = 18 261
Age, mean (SD)*	83.0 (7.1)	79.3 (7.4)
Male*	39.7%	44.0%
Race and ethnicity		
Caucasian*	93.5%	91.0%
Black and/or Hispanic*	4.7%	7.4%
Asian or other race	1.8%	1.6%
Warfarin at discharge*	33.5%	48.9%
Discharged to nursing home*	43.1%	21.2%
Terminal disease	0.56%	0.71%
Bleeding risk factors (mean number)*	2.5	1.7
Anemia*	18.2%	16.0%
Thrombocytopenia or bleeding disorder*	5.3%	4.0%
Chronic renal disease	6.2%	6.0%
Aspirin use*	37.8%	29.7%
Uncontrolled hypertension	2.9%	2.7%
Malignancy*	6.4%	8.0%
Alcohol abuse*	5.0%	3.0%
Rebleeding risk (ie, prior bleed)*	28.8%	25.7%
Increased age (> 75)*	87.4%	71.9%
Neuropsychiatric impairment*	36.1%	13.9%
Stroke/TIA history*	46.1%	28.5%

TIA is transient ischemic attack.

**P* < 0.05.

were coded after the baseline hospitalization. Compared to other patients, patients at high risk for falls were 2.0 (95% CI: 1.6–2.4) times more likely to fall. The rates of fractures per 100 patient-years were 27.9 in patients at high risk for falls and 12.0 in other patients.

Intracranial hemorrhage

The rates (Table 2) of intracranial hemorrhage per 100 patient-years were 2.8 (95% CI: 1.9–4.1) in patients at high risk for falls and 1.1 (95% CI: 1.0–1.3) in other patients (*P* < 0.0001, log-rank test). In the subset of the trial-like patients, the rate of intracranial hemorrhage was 0.53 (95% CI: 0.3–0.8). The rates of traumatic intracranial hemorrhage per 100 patient-years were 2.0 (95% CI: 1.3–3.1) in patients at high risk for falls and 0.34 (95% CI: 0.27–0.45) in other patients (*P* < 0.0001, log-rank test).

In the multivariate Cox model (Table 3), patients at high risk for falls were 1.9 (95% CI 1.3–2.9) times more likely to have any intracranial hemorrhage and 4.1 (95% CI 2.4–7.1) times more likely to have a traumatic intracranial hemorrhage than other patients. Prior stroke (HR 2.2), prior major bleeding (HR 1.8), and neuropsychiatric impairment (HR

1.4) also were independently associated with any intracranial hemorrhage (Table 3). Prescription of warfarin or aspirin at baseline did not significantly affect risk of intracranial hemorrhage: the HR for warfarin was 1.0 (95% CI 0.8–1.4) and the HR for aspirin was 1.1 (95% CI 0.8–1.4). Alcohol abuse, non-Caucasian race, bleeding disorder, and renal disease were too infrequent in the dataset to quantify their effects.

After an intracranial hemorrhage, 30-day mortality was 42% in patients at high risk of falls and 48.2% in other patients ($P > 0.2$). The intracranial hemorrhage 30-day mortality was 51.8% in patients who had been prescribed warfarin, and 33.6% in patients who had not been prescribed warfarin after the baseline hospitalization ($P = 0.007$). In a stepwise logistic regression model, the only independent predictors of 30-day mortality post intracranial hemorrhage were prior prescription of warfarin (odds ratio 2.5; 95% CI 1.4–4.5, $P = 0.002$) and nursing home residency (odds ratio 3.3; 95% CI 1.6–6.8, $P = 0.0009$).

Ischemic stroke

Stroke rates (95% CI) per 100 patient-years were 13.7 (11.6–16.3) in patients at high risk for falls and 6.9 (6.5–7.3) in other patients. In the subset of the trial-like patients, the stroke rate was 2.8 (95% CI: 2.3–3.4). Compared to other patients, patients at high risk for falls had a 1.3-fold (95% CI: 1.1–1.6) increased risk of stroke ($P = 0.002$). Each 1-point increase in the CHADS₂ score increased the risk of stroke by a factor of 1.42 (95% CI: 1.37–1.47, $P < 0.0001$). Hazard ratios (HR) and 95% CI of other independent stroke risk factors were neuropsychiatric impairment 1.22 (1.06–1.40, $P = 0.05$) and nursing home residence 1.45 (1.29–1.64, $P < 0.0001$); warfarin prescription at hospital discharge had a modestly protective effect 0.78 (0.70–0.86, $P < 0.0001$). After stroke, 30-day mortality was 34.4% among high-fall-risk subjects, 27.8% in other patients, and 21.8% in the trial-like cohort.

Table 2 Rates of intracranial hemorrhage, stratified by cohort

Intracranial hemorrhage rate (95% CI) per 100 patient-years		
Intracranial hemorrhage type	High-fall-risk patients (n = 1245)	Other patients (n = 18 261)
Traumatic	2.0 (1.3–3.1)*	0.34 (0.27–0.45)
Nontraumatic	0.7 (0.4–1.5)	0.8 (0.7–0.9)
Total*	2.8 (1.9–4.1)†	1.1 (1.0–1.3)

* $P < 0.0001$ High-fall vs other patients.

† $P = 0.0005$ High-fall vs other patients.

Table 3 Multivariate Cox regression showing hazard ratios (HR) of independent predictors of intracranial hemorrhage

Factor	HR (95% CI)	P Value
High-risk for falls	1.9 (1.3–2.9)	0.002
Prior stroke	2.2 (1.7–2.8)	<0.0001
Prior bleed	1.8 (1.4–2.4)	<0.0001
Neuropsychiatric impairment	1.4 (1.0–1.9)	0.055

Risks and benefits of warfarin therapy in patients at high risk for falls

To determine the potential benefit of prescribing warfarin in patients at high risk for falls, we quantified the association between warfarin use and the composite outcome of hospitalization for stroke, any hemorrhage (including intracranial hemorrhage), myocardial infarction, or out-of-hospital death (except in patients with terminal disease). In the Cox model that controlled for bleeding risk factors, aspirin prescription, nursing home residency, and sex, warfarin was significantly protective in 1086 patients with 2 or more CHADS₂ points (HR 0.75), but not protective in 159 patients with 0 or 1 points in (HR 0.98) (Table 4). The P -value for interaction between warfarin and stroke risk was not significant ($P = 0.31$).

Discussion

Despite their low use of warfarin (33.5%), patients at high risk for falls suffered 2.8 intracranial hemorrhages per 100 patient-years, more than twice the 1.1 intracranial hemorrhage rate of other participants and more than 5 times the 0.5 rate of trial-like participants. The increased risk of intracranial hemorrhage in patients at high risk for falls was due to their increased incidence of traumatic intracranial hemorrhage, which was increased four-fold compared to other patients, even after adjusting for the covariates. The 30-day mortality after an intracranial hemorrhage was sig-

Table 4 Hazard ratio of warfarin for composite outcome—out-of-hospital death or hospitalization for stroke, myocardial infarction, or hemorrhage—in 1245 patients at high risk for falls

CHADS ₂ score	Hazard ratio (95% CI)	P value	Recommended antithrombotic therapy
0–1	0.98 (0.56,1.72)	0.94	Aspirin or nil
2–6	0.75 (0.61,0.91)	0.004	Anticoagulant

CHADS₂ stroke score was calculated by adding 1 point for each of the following conditions: congestive heart failure, hypertension, age > 75 years, or diabetes and 2 points for a prior stroke or transient ischemic attack. CI indicates confidence interval.

nificantly greater in patients who had been prescribed warfarin after the baseline hospitalization (51.8%) than in patients who had not been prescribed warfarin (33.6%). These observations highlight the substantial risk and mortality of intracranial hemorrhage in populations who are older and frailer than carefully selected trial participants.

Despite the significant association between intracranial hemorrhage and fall risk, the findings support the use of anticoagulants in patients at high risk for falls who are at moderate to high risk of stroke. Prescribing warfarin in patients at high risk for falls with 2 or more CHADS₂ points was associated with a 25% relative risk reduction (HR 0.75) in the composite outcome (Table 4). When prescribing warfarin to these patients, providers could instruct them to take precautions to limit their risk of falling: wear stable shoes,²¹ exercise regularly,²² take vitamin D,²³ use walking aids,²⁴ and discontinue unnecessary medications.²⁴⁻²⁶

In contrast to the potential benefits of warfarin in patients with greater CHADS₂ scores, prescribing warfarin in patients at high risk for falls with 0 or 1 CHADS₂ points was associated with a nonsignificant reduction in the composite outcome (Table 4). Because the 95% confidence interval of the HR (0.98) was wide (0.59–1.72), warfarin could either be beneficial or harmful in this population. Given this uncertainty and the known expense, hassle, and risks of warfarin therapy, we recommend aspirin or no antithrombotic therapy for this population.

Besides fall risk, prior stroke, prior bleeding, and neuropsychiatric impairment were associated with incident intracranial hemorrhage. Others also have found an association between prior stroke and intracranial hemorrhage.^{27,28} The mechanism behind this association may be loss of microvascular integrity or disruption of neurovascular homeostasis. Patients with a history of epistaxis are more likely to have an intracranial hemorrhage,²⁹ and patients with a prior intracranial hemorrhage, especially a primary lobar intracranial hemorrhage, are at increased risk of recurrence.³⁰ The association between intracranial hemorrhage and neuropsychiatric disease may depend on the type of neuropsychiatric disease and the degree of impairment in performance status.³¹ Psychiatric disease may cause falls because of treatment with psychotropic medications,^{25,26} associated alcohol use, or poor compliance. Patients with Parkinson's disease can fall because of a festinating gait.³² Patients with Alzheimer's dementia may be predisposed to intracranial hemorrhage if they have cerebral amyloid angiopathy or certain apolipoprotein E polymorphisms.³³⁻³⁵

This study has limitations inherent to use of administrative data. First, because all participants were deidentified, we were not able to validate the diagnosis of intracranial hemorrhage by reviewing brain-imaging studies. However, the ICD-9 codes we used to identify intracranial hemorrhage have a specificity of over 99%.¹⁷ Had we corrected for the known misclassification rate of ICD-9 codes for intracranial hemorrhage, incidence rates would be increased by a factor of 1.26. A second limitation is that we knew

what antithrombotic therapy was prescribed at hospital discharge but did not capture subsequent initiation or discontinuation of therapy. Thus, the observed lack of association between warfarin and intracranial hemorrhage in this study does not refute such an association.^{36,37} A third limitation is that we had to exclude patients who died after the baseline hospitalization and without another hospitalization because they had no follow-up data. A minor limitation was that we could not evaluate risk factors for intracranial hemorrhage that were unavailable (eg, leukoaraiosis on brain imaging or tobacco use). Likewise, we used physician documentation to ascertain risk of falls and were unable to evaluate the risk of specific impairments in strength, balance, vision, or orthostasis.³²

These limitations are offset by several strengths. First, the cohort design allowed us to calculate incidence rates and to avoid recall bias. Second, we were able to use structured medical record abstraction to adjust for potential confounding factors. Third, the large size and national sample of the dataset provide great generalizability. Fourth, the designation "high-fall-risk" predicted subsequent fractures and falls, validating the designation. The specificity between the relationship between high-fall-risk and traumatic intracranial hemorrhage validates the association.

In summary, patients at high risk for falls are at substantially increased risk of intracranial hemorrhage, especially traumatic intracranial hemorrhage. However, because of their increased risk of stroke, they appear to benefit from anticoagulant therapy if they have atrial fibrillation and at least 2 CHADS₂ points.

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