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Death and Disability from Warfarin-Associated Intracranial and Extracranial Hemorrhages

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Abstract

OBJECTIVES—Little is known about the outcomes of patients who have hemorrhagic complications while receiving warfarin therapy. We examined the rates of death and disability resulting from warfarin-associated intracranial and extracranial hemorrhages in a large cohort of patients with atrial fibrillation.

METHODS—We assembled a cohort of 13,559 adults with nonvalvular atrial fibrillation and identified patients hospitalized for warfarin-associated intracranial and major extracranial hemorrhage. Data on functional disability at discharge and 30-day mortality were obtained from a review of medical charts and state death certificates. The relative odds of 30-day mortality by hemorrhage type were calculated using multivariable logistic regression.

RESULTS—We identified 72 intracranial and 98 major extracranial hemorrhages occurring in more than 15,300 person-years of warfarin exposure. At hospital discharge, 76% of patients with intracranial hemorrhage had severe disability or died, compared with only 3% of those with major extracranial hemorrhage. Of the 40 deaths from warfarin-associated hemorrhage that occurred within 30 days, 35 (88%) were from intracranial hemorrhage. Compared with extracranial hemorrhages, intracranial events were strongly associated with 30-day mortality (odds ratio 20.8 [95% confidence interval, 6.0–72]) even after adjusting for age, sex, anticoagulation intensity on admission, and other coexisting illnesses.

CONCLUSIONS—Among anticoagulated patients with atrial fibrillation, intracranial hemorrhages caused approximately 90% of the deaths from warfarin-associated hemorrhage and the majority of disability among survivors. When considering anticoagulation, patients and clinicians need to weigh the risk of intracranial hemorrhage far more than the risk of all major hemorrhages.

Keywords

Atrial fibrillation; Death; Disability; Hemorrhage; Intracranial hemorrhage; warfarin

Atrial fibrillation is the most common clinically significant cardiac arrhythmia and increases the risk for ischemic stroke 4- to 5-fold.¹ Anticoagulation therapy with warfarin can reduce the risk for ischemic stroke by 68% but also increases the risk for major hemorrhagic complications.² Clinical decision-making regarding the appropriateness of warfarin therapy for patients with atrial fibrillation has generally relied on balancing the risk of ischemic strokes without warfarin therapy with the risk of all major hemorrhage with warfarin therapy.

Rates of ischemic stroke in patients with atrial fibrillation who are not taking warfarin can be as high as 12% per year,^{2,3} and the proportion of patients who have major functional disability after an atrial fibrillation-related ischemic stroke is substantial, as high as 59%.⁴ Yet multiple studies demonstrate that patients with atrial fibrillation are frequently not prescribed warfarin despite its benefits in ischemic stroke risk reduction.⁵⁻⁷ The primary deterrent to prescribing warfarin is the fear of inducing life-threatening hemorrhage.⁸

Although concerns about hemorrhage prevent many patients from receiving warfarin, there are relatively little data about the actual rates of death and disability resulting from warfarin-associated hemorrhage, particularly among patients with atrial fibrillation and using current targets of anticoagulation intensity. Although intracranial hemorrhages are widely considered more severe than extracranial hemorrhages, few studies have been able to quantify the actual differences in outcomes between intracranial and extracranial types of hemorrhage. Most studies lacked sufficient numbers of hemorrhagic events to examine the differences in mortality and morbidity; for example, a pooled analysis of 5 randomized trials of warfarin for atrial fibrillation reported a total of only 6 intracranial hemorrhages occurring with warfarin therapy.² Our objective was to quantify the risk of death and major disability occurring from warfarin-associated intracranial and extracranial hemorrhages. Such information should allow for more rational choices about the appropriateness of warfarin therapy in patients with atrial fibrillation.

METHODS

Cohort Assembly and Ascertainment of Patient Characteristics

The Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study is a cohort of 13,559 adults with diagnosed nonvalvular atrial fibrillation who received care within Kaiser Permanente of Northern California, a large integrated health care delivery system. Details of the cohort assembly have been described.⁹ Cohort members were identified by searching automated inpatient, outpatient, and electrocardiographic databases for physician-assigned International Classification of Diseases, Ninth Revisions, Clinical Modification diagnoses of atrial fibrillation (427.31) between July 1, 1996, and December 31, 1997. Because we were interested in nontransient, nonvalvular atrial fibrillation, we excluded patients with atrial fibrillation and diagnosed mitral stenosis, valvular repair or replacement, transient postoperative atrial fibrillation, or concurrent hyperthyroidism.

The cohort was followed through August 31, 1999, providing a median follow-up of 2.4 years (interquartile range 1.8–2.8 years). Data on patient age and sex were obtained from administrative databases, and data on comorbid medical conditions were collected from validated clinical inpatient and ambulatory databases.⁹ To specifically address warfarin-associated hemorrhage, we restricted our analyses to periods of time in which patients were exposed to warfarin, as determined using a previously validated algorithm.⁹

Hemorrhagic Events

We identified potential hemorrhagic events by searching comprehensive automated hospitalization and billing databases for primary and secondary discharge diagnoses of

intracranial hemorrhage, and for primary diagnoses of gastrointestinal and other non-intracranial hemorrhages.¹⁰ Warfarin exposure was confirmed through review of the admission medical record. We searched only for primary diagnoses of extracranial hemorrhage, because in a review of 110 randomly selected hospitalizations with only a secondary discharge diagnosis of extracranial hemorrhage, only 4.4% of these were valid major hemorrhagic events. Intracranial hemorrhages were categorized as intracerebral, subdural, or other (eg, subarachnoid) on the basis of radiology reports obtained from the medical records. Intracranial hemorrhages caused by significant head trauma (eg, from antecedent neurosurgery) were excluded. We defined major extracranial hemorrhage as fatal, requiring transfusion of 2 or more units of packed red blood cells, or hemorrhage into a critical anatomic site, such as the retro-peritoneum. To restrict analyses to the most serious hemorrhages, events not leading to hospitalization or death were excluded. Because Kaiser Permanente is an integrated health care network, cohort members admitted to facilities outside of the network were still identified by our search strategy.

The emergency department and hospitalization medical records for each potential event were reviewed by a 3-physician Clinical Outcomes committee. Each event was independently validated by 2 physicians on the committee using a formal study protocol, and disagreements were resolved by a consensus of all 3 committee members. The international normalized ratio (INR) at presentation and before reversal of anticoagulation was obtained from medical records, emergency department records, or the inpatient health plan laboratory database.

Each patient's functional disability at the time of discharge was determined on the basis of a physician's review of the medical records, including review of documentation from physician, nursing, physical/occupational therapy, and social work services. Functional disability at the time of discharge was categorized using a modified Rankin scale¹¹; the categories were fatal inpatient event, major disability (ie, deficit that prevented independent living), minor disability (ie, residual deficit that did not interfere with independent living), and no disability. This assessment of functional disability has been strongly associated with subsequent death within 30 days in patients admitted with atrial fibrillation-associated ischemic stroke.⁴ For 13 patients, the available clinical information was insufficient to determine the extent of functional impairment, and these patients were excluded from the analysis of disability. Deaths during the hospitalization and at 30 days after the event were determined through reviewing medical charts, health plan databases, and the comprehensive California State death certificate registry.¹² Data on mortality were complete for all patients.

Statistical Analyses

Incidence rates of intracranial and major extracranial hemorrhage were calculated as the number of events occurring per 100 person-years of follow-up. We compared functional disability at discharge between patients with intracranial versus extracranial hemorrhagic events using the chi-squared test for categorical variables. We then used multivariable logistic regression to quantify the relative impact of intracranial versus extracranial hemorrhage on 30-day mortality, adjusted for age, INR, and comorbid conditions. To avoid potential overfitting of the model, we included in the multivariable model only comorbid conditions that differed between patients with intracranial and extracranial hemorrhages at a *P* value of less than .1 on bivariate analyses.

All analyses were conducted using SAS statistical software, version 9.1 (Cary, NC). This study was approved by institutional review boards of the collaborating institutions.

RESULTS

During the study period, we identified 72 patients hospitalized with a validated warfarin-associated intracranial hemorrhage during 15,370 person-years of follow-up on warfarin therapy (unadjusted annualized rate 0.47%, 95% confidence interval [CI], 0.37%–0.59%). Of these, 51 (71%) were intracerebral, 15 (21%) were subdural, and 6 were other or unknown types of intracranial hemorrhages. We also identified 98 patients with a validated warfarin-associated major extracranial hemorrhage during 15,306 person-years of follow-up (annualized rate 0.64%, 95% CI, 0.53%–0.78%). Of these, 87 (89%) involved the gastrointestinal tract. The median age did not differ significantly for patients with intracranial hemorrhage compared with extracranial hemorrhage (Table 1). Compared with patients sustaining an intracranial hemorrhage, more patients with extracranial hemorrhages were female, had a history of diabetes and prior gastrointestinal bleed, and had higher median INRs at presentation, although these comparisons did not reach statistical significance (Table 1).

Outcomes After Major Hemorrhage

Although the overall mortality rate from warfarin-associated hemorrhage was low, the majority of deaths occurred from intracranial hemorrhage. Of the 40 patients who died from warfarin-associated hemorrhage, 35 (88%) died of intracranial hemorrhage (annualized mortality rate of 0.23% [95% CI, 0.16%–0.32%]) and only 5 died of major extracranial hemorrhage (annualized mortality rate 0.03% [95% CI, 0.01%–0.08%]) ($P<.001$, Figure 1). Intracranial hemorrhage continued to be strongly associated with 30-day mortality compared with extracranial hemorrhage even after adjusting for differences in other covariates (age, sex, diabetes mellitus, prior gastrointestinal bleed, and INR at presentation), with an adjusted odds ratio of 20.8 [95% CI, 6.0–72.2]. Among patients sustaining an intracranial hemorrhage, intracerebral hemorrhages resulted in a higher case fatality than subdural hemorrhage (60.1% vs 26.7%, respectively, $P=.04$).

At the time of hospital discharge, patients with intracranial hemorrhage had far more severe functional deficits than did patients with major extracranial hemorrhage (Figure 2). With the exclusion of 13 patients whose discharge disability was unavailable, 26 patients (42%) with intracranial hemorrhage had a fatal inpatient event compared with only 2 patients (2%) with extracranial hemorrhages. Among the 129 survivors at the time of discharge, 21 patients (61%) with an intracranial hemorrhage had major functional disability compared with only 1 patient (1%) with a major extracranial hemorrhage ($P<.001$). Moreover, among the 21 patients who had major disability from intracranial hemorrhage at the time of discharge, 7 died within 30 days.

DISCUSSION

Intracranial hemorrhages accounted for approximately 90% of the deaths caused by warfarin-associated hemorrhage, and most of the functional disability among survivors in this cohort of patients taking warfarin for atrial fibrillation. Although the overall rate of hemorrhagic events in the cohort was relatively low, of those patients who sustained a complication from warfarin, intracranial hemorrhage was the primary determinant of death and disability.

The approximately 50% mortality rate from warfarin-associated intracranial hemorrhage in this study is comparable to that observed in other settings.^{13–16} Although intracranial hemorrhages are generally rare events, the adverse consequences resulting from them are considerably higher than those observed from the more common extracranial hemorrhage events. Extracranial hemorrhages, primarily of gastrointestinal origin in this study, are more

likely to be remediable events, making residual deficits uncommon. The overall rate of fatal hemorrhage in this present study approximates the rates reported in a recent study from the Leiden Anticoagulation clinic, although that study was not restricted to patients with atrial fibrillation, used higher INR target ranges, and did not examine bleeding-related disability.¹⁷

Data on the expected outcomes from warfarin-associated hemorrhage are vital to improving how clinicians and patients decide on the use of antithrombotic therapy for atrial fibrillation. Atrial fibrillation-related ischemic stroke is associated with a significant risk of death and major disability, with worse outcomes if the strokes occur while the patient is not taking warfarin.⁴ These risks must be balanced against the risk and impact of warfarin-associated hemorrhage. Previous studies generally weighed the risk of ischemic stroke against the risk of all major hemorrhages. Our data demonstrate that it is intracranial hemorrhage that overwhelmingly determines poor outcomes from warfarin, and as a result, the risk of non-intracranial hemorrhage should have a relatively small effect on decisions about warfarin therapy in atrial fibrillation. Although extracranial hemorrhages certainly result in hospitalizations, invasive procedures, and discontinuation of antithrombotic therapy,¹⁸ the longer-term functional impact of such hemorrhages is generally much less than that of intracranial hemorrhages or ischemic strokes. Investigations by Devereaux and colleagues¹⁹ reveal that patients are much more willing than physicians to accept a far higher risk of gastrointestinal hemorrhage in return for an associated reduction in the risk of stroke.

The rates of intracranial hemorrhage on warfarin observed in our study were still considerably lower than the rates of ischemic stroke while the patient was not taking warfarin. As previously reported, the rate of thromboembolism occurring without warfarin therapy was 2.5 per 100 person-years in the overall ATRIA cohort¹⁰ and even higher in other cohorts^{2,20–22}; these rates are reduced by more than 50% by warfarin therapy.^{10,23} This benefit exceeds the additional risk of warfarin-associated intracranial hemorrhage (0.47 per 100 person-years with warfarin therapy compared with 0.29 per 100 person-years without warfarin therapy),^{10,24} and the balance of risk to benefit seems to favor the use of warfarin for the typical patient with atrial fibrillation.² Nevertheless, there are likely to be subgroups of patients with atrial fibrillation for whom this balance is less favorable, making further work to identify these subgroups critical to optimizing the use of warfarin at the individual and population levels.

The infrequency of intracranial hemorrhage makes a priori prediction challenging for the individual patient. Older age, elevated INR level, and history of ischemic stroke have all been identified as risk factors for intracranial hemorrhage, but because older age and prior stroke are also risk factors for ischemic stroke, additional investigation into unique risk factors for intracranial hemorrhage is clearly needed.^{2,15,24} Modifiable measures, such as maintaining anticoagulation intensity within the therapeutic range of INR 2.0 to 3.0, can reduce but will not entirely remove the risk of bleeding associated with warfarin.^{15,25} A study of Medicare patients with atrial fibrillation showed that a high fall risk was associated with an increased risk of intracranial hemorrhage,¹⁶ although the high rate of ischemic stroke (13.7 per 100 person-years) among this subset of patients with a high fall risk made warfarin the preferred option for most patients. Some evidence suggests that testing for the apolipoprotein E genotype or detecting cerebral amyloid angiopathy and leukoaraiosis on brain imaging studies might help refine existing prediction rules for hemorrhage.^{26–28} Future validation of the effectiveness of incorporating such predictors into clinical practice is clearly needed to help improve current risk stratification for intracranial hemorrhage.

Our study was strengthened by including the largest number of validated warfarin-related hemorrhages among patients with atrial fibrillation reported to date. Patients were managed using current INR targets, and there was comprehensive assessment of relevant clinical

features and subsequent outcomes. However, our study also had several limitations. As an observational study of actual clinical practice, clinicians in our study may have selectively avoided prescribing warfarin to patients at the highest risk for poor outcomes from extracranial hemorrhages. Our observations took place in a health care setting where anticoagulation was predominantly managed by centralized anticoagulation clinics, which may better maintain anticoagulation levels in a therapeutic range.^{29,30} However, it is unlikely that these limitations would invalidate the markedly more severe impact of intracranial compared with extracranial hemorrhages. Finally, it is possible that our screening strategy, which identified only hospitalizations for a primary diagnosis of extracranial hemorrhage, could have missed some extracranial hemorrhage events, although prior validation studies of the ATRIA cohort indicate that these exclusions missed only a small fraction of the total number of major extracranial bleeds.¹⁰

CONCLUSION

Intracranial hemorrhages are the primary determinant of poor outcomes from warfarin-associated hemorrhage, resulting in substantially higher rates of death and disability than major extracranial hemorrhages. As a consequence, rather than basing the anticoagulation decision on a patient's risk for hemorrhage of all types, clinicians should depend primarily on a comparison of the patient's ischemic stroke risk without warfarin therapy with the risk of intracranial hemorrhage with warfarin therapy. Further work is needed to develop better ways to identify patients at the greatest risk for intracranial hemorrhage and more effective methods to mitigate its severe consequences.

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CLINICAL SIGNIFICANCE

- Warfarin-associated intracranial hemorrhages are uncommon but substantially more lethal than other types of warfarin-associated bleeding.
- Because extracranial hemorrhages rarely lead to death or significant disability, the risk for extracranial hemorrhages should be less emphasized when considering the use of oral vitamin K antagonists to prevent stroke in patients with atrial fibrillation.
- Our results highlight the critical need to find better predictors of intracranial hemorrhage and improve risk stratification in individual patients.

Figure 1.

Risk of death 30 days after hospitalization for warfarin-associated intracranial hemorrhage versus major extracranial hemorrhage; 95% confidence intervals (CIs) (*vertical bars*). *P* value refers to the chi-square comparison of mortality rate of intracranial versus extracranial hemorrhage.

Figure 2.

Functional deficit at the time of discharge resulting from warfarin-associated intracranial hemorrhage versus major extracranial hemorrhage in hospitalized patients with atrial fibrillation. *P* value refers to chi-square comparison of discharge deficit between intracranial and extracranial hemorrhage events. Analysis excludes 13 patients whose discharge deficit was not known.

Table 1

Comparison of Clinical Characteristics of Patients with Nonvalvular Atrial Fibrillation Who Were Hospitalized for Intracranial Hemorrhage vs Major Extracranial Hemorrhage While Receiving Warfarin Therapy

Characteristic	Intracranial (n = 72)	Extracranial (n = 98)	P value
Median age (interquartile range)	77 (69–82)	77 (71–79)	.6
Female (%)	32	45	.09
Prior stroke (%)	25	19	.4
Prior gastrointestinal bleed (%)	5	14	.07
Congestive heart failure (%)	42	54	.1
Hypertension (%)	67	68	.8
Coronary artery disease (%)	35	46	.2
Diabetes mellitus (%)	19	33	.06
Median INR (interquartile range)	2.7 (2.3–4.0)	3.4 (2.2–5.1)	.1