Warfarin-associated Intracerebral Hemorrhage is Increasing in Prevalence in the United States

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Background: Warfarin-associated intracerebral hemorrhage (WAICH) is expected to increase in prevalence as the population ages. We sought to evaluate national trends, characteristics, and in-hospital outcomes among intracerebral hemorrhage (ICH) patients taking warfarin at baseline. *Methods:* We reviewed the Nationwide Inpatient Sample to identify all admissions with primary diagnosis of ICH by *International Classification of Diseases, Ninth Revision* code (431) from 2005 to 2008. We identified premorbid warfarin use by the V code (V58.93) and calculated the proportion of WAICH among all ICH patients in each year. We employed univariate statistics and generalized estimating equation regression models to assess whether warfarin use independently increased the risk of in-hospital mortality after adjusting for relevant covariates. *P* value less than .05 was considered significant. *Results:* There were 52,993 patients (mean age 68.8 years; 49.7% male) coded for ICH between 2005 and 2008. The proportion with WAICH increased each year (2005, 5.8%; 2006, 6.5%; 2007, 6.9%; 2008, 7.3%; *P* < .001). While in-hospital mortality declined each year for non-WAICH (29.0%-25.4%, *P* < .001), it remained unchanged for WAICH (42.1%-40.0%, *P* = .346). In multivariable analysis, warfarin use (adjusted odds ratio 1.35; 95% confidence interval 1.24-1.47) remained an independent predictor of in-hospital mortality. *Conclusions:* WAICH is increasing in prevalence in the United States and is associated with a 35% higher mortality than non-WAICH. While mortality has declined over time for non-WAICH, mortality after WAICH is unchanged. Specific strategies to decrease the mortality of WAICH such as rapid reversal of anticoagulation are warranted. **Key Words:** Anticoagulation—intracerebral hemorrhage—warfarin—coagulopathy.
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Warfarin-associated intracerebral hemorrhage (WAICH) is expected to become more prevalent as the population ages and the number of chronically ill patients increases.[1] The high morbidity and mortality associated with WAICH[2] in combination with increasing prevalence suggests that WAICH will present a growing challenge.

A prior study of regional patterns suggested that the incidence of WAICH increased during the 1990s in the Cincinnati, OH, area.[1] During the same period, intracerebral hemorrhage (ICH) mortality improved.[3] However, it is unclear if WAICH prevalence and mortality is changing on a national scale in the United States compared to the non-WAICH population. We sought to evaluate national trends in the proportion of WAICH and in-hospital outcomes between 2005 and 2008 and to determine if premorbid warfarin use independently increased the risk of in-hospital mortality following ICH.

Methods

We used the Nationwide Inpatient Sample (NIS), the largest all-payer inpatient database in the United States,[4] and *International Classification of Diseases, Ninth Revision*

(*ICD-9*) code for ICH (431) to identify and collect demographic data for all admissions with a primary diagnosis of ICH between 2005 and 2008. We identified patients with premorbid or current warfarin use by the V code, V58.93. By cross-referencing the *ICD-9* code and V code we were able to identify WAICH patients and calculate the proportion of ICH discharges associated with warfarin use in each year. We determined in-hospital mortality for both WAICH and non-WAICH and compared the differences in mortality for each group and over time. We also identified all admissions with a primary diagnosis of multiple sclerosis (MS), using *ICD-9* code 340, and cross-referenced these admissions with the warfarin V code to determine the proportion of MS admissions with concurrent warfarin use; since MS is not likely to be specifically associated with a need for anticoagulation or with the trend toward an aging population, any change in documentation of the warfarin V code over time in this population would suggest a change in V-code compliance rather than a genuine increase in the use of warfarin. Chi-square tests and Student *t* tests were used as appropriate in univariable analysis. The Cochrane-Armitage test was used to test trends.

Available covariates in the NIS include demographics, source and day of admission, up to 15 diagnoses and procedures, hospital costs, and discharge disposition. We selected the following 12 candidate variables and developed a multivariable generalized estimating equation model of in-hospital mortality: age, warfarin use, mechanical ventilation within 96 hours of admission, comorbid coagulopathy, coronary artery disease, congestive heart failure, year of admission, weekend admission, region of the United States, insurance status, race, and sex. These were selected based on univariable analysis and plausibility as a risk factor for mortality. We used *ICD-9* procedure code 96.7 to identify mechanically ventilated patients, which was included in the model as a surrogate measure of hemorrhage severity. Comorbid coagulopathy (*ICD-9* codes 286.0-286.9, 287.1, 287.3-287.5, 289.81-289.82), which includes such illnesses as congenital and acquired coagulation factor deficiencies, antiphospholipid antibody syndrome, and thrombocytopenia and disorders of platelet dysfunction, was included so as to account for patients whose outcomes may be dictated by a mechanism similar to WAICH, namely a propensity toward larger hematoma volumes. Coronary artery disease and congestive heart failure were included in the model since there is evidence that cardiac disease contributes to early and late mortality following ICH.[5,6] A generalized estimating equation model was used to account for hospital clustering effect. *P* value less than .05 was considered significant and all statistical analyses were performed using software (SPSS 16.0, IBM Corp, Armonk, NY).

Results

Between 2005 and 2008 there were 52,993 patients admitted to US hospitals with a primary diagnosis of ICH. Of these, 3495 (6.6%) had V-code documentation for premorbid or baseline warfarin use and were considered WAICH. WAICH patients were significantly older (75.5 versus 68.8 years; *P* < .001) and predominately caucasian. Table 1 summarizes patient demographics and characteristics of WAICH as compared to non-WAICH patients.

The proportion of warfarin use among ICH patients increased annually (2005, 5.8%; 2006, 6.5%; 2007, 6.9%; 2008, 7.3%; *P* < .001) while the proportion of MS admissions with concurrent warfarin use did not change over time (2005, 0.8%; 2006, 1.1%; 2007, 1.0%; 2008, 1.1%; *P* = .49). Overall, in-hospital mortality for WAICH was 40.3% versus 26.6% for non-WAICH. Figure 1 shows the mortality of WAICH and non-WAICH each year. In-hospital mortality declined each year in non-WAICH (*P* < .001) but remained unchanged for WAICH (*P* = .346).

In multivariable analysis of predictors of in-hospital mortality (Table 2), warfarin remained an independent predictor of in-hospital mortality (adjusted odds ratio [OR] 1.35; 95% confidence interval [CI] 1.24-1.47; *P* < .001). Mechanical ventilation within the first 96 hours of admission (adjusted OR 3.22; 95% CI 3.07-3.38; *P* > .001), increasing age (adjusted OR 1.016; 95% CI 1.014-1.018; *P* < .001), comorbid coagulopathy (adjusted OR 1.29; 95% CI 1.17-1.42; *P* < .001), and coronary artery disease (adjusted OR 1.14; 95% CI 1.07-1.20; *P* < .001) were also strong predictors of increased mortality.

Discussion

Our analysis showed that WAICH increased from 5.8%-7.3% of ICH admissions in the United States between 2005 and 2008. These findings extend the findings of regional studies in the 1990s[1] to a national scale. Since the NIS accounts for approximately 20% of all US hospital admissions,[4] we estimate there were over 4800 WAICH hospitalizations in 2008. The increasing proportion of WAICH may in part be due to the greater prevalence of atrial fibrillation[7] as well as a general increase in the number of chronically ill individuals. Our results are within the 4%-18.5% range reported in the literature.[1,8-10] It may be that this wide range of WAICH is due to regional differences in medical practice and population characteristics that create pockets of relatively higher or lower WAICH. For example, urban areas with larger proportions of blacks may be less likely to receive anticoagulation for atrial fibrillation.[11] Indeed, a cohort study performed during the same study period as ours observed that WAICH accounted for 8% of ICH in Chicago, IL.[8]