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Intracranial hemorrhage mortality in atrial fibrillation patients treated with dabigatran or warfarin

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Abstract

Background and purpose—In randomized trials, atrial fibrillation (AF) patients receiving dabigatran, a direct oral anticoagulant, had lower risk of intracranial bleeding (ICB) than those on warfarin. However, concerns exist about potential worse outcomes in dabigatran users if bleeding occurs, given the lack of approved reversal agents. Thus, we examined in-hospital mortality in AF patients with ICB being treated with dabigatran vs warfarin in a real-world population in the United States.

Methods—We analyzed healthcare utilization claims in the Truven Health Marketscan® Research Databases. The study sample included AF patients admitted to a hospital with a primary diagnosis of ICB. Information on medications, inpatient, and outpatient diagnoses was obtained from available claims. Propensity score-adjusted risk ratios (RR) and 95% confidence intervals (95%CI) of in-hospital mortality comparing current users of dabigatran versus warfarin were estimated using relative risk regression.

Results—Among 2391 AF patients admitted with ICB (2290 on warfarin, 101 on dabigatran), 531 died during their admission. In-hospital mortality was similar in those treated with warfarin (22%) or dabigatran (20%). Compared to warfarin users, the propensity score-adjusted RR (95%CI) of mortality in dabigatran users was 0.93 (0.62, 1.37). Associations were similar across different ICB subtypes (intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematoma).

Conclusion—In this sample of AF patients on oral anticoagulants with ICB, dabigatran was not associated with higher in-hospital mortality compared to warfarin. Hence, reluctance to use of dabigatran because of a lack of approved reversal agents is not supported by our results.

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DISCLOSURES

None

Keywords

atrial fibrillation; warfarin; dabigatran; intracranial hemorrhage

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with an increased risk of ischemic stroke and other cardiovascular diseases.[1] Current guidelines for its treatment recommend chronic oral anticoagulation in patients with at least a moderate risk of ischemic stroke.[2] Until recently, the only available drugs for oral anticoagulation in AF were vitamin K antagonists (mostly warfarin in the United States). This landscape has changed in the last few years, with the approval by the Food and Drug Administration of 3 new oral anticoagulants (NOAC) for the prophylaxis of ischemic stroke and other cardioembolic complications. These new drugs—the direct thrombin inhibitor dabigatran and the direct factor X inhibitors rivaroxaban and apixaban—have been shown to be non-inferior or superior to warfarin with respect to the prevention of stroke, while being associated in general with lower rates of hemorrhage, particularly intracranial bleeding (ICB).[3–5]

In contrast to warfarin, the NOACs lack approved, commercially-available antidotes that could reverse their anticoagulant effect in case of acute hemorrhage (though there are several in different stages of development). This limitation has been highlighted as a major disadvantage of the new drugs.[6] The main concern is that absence of specific reversal agents would increase the severity of any bleeding, resulting in higher mortality and overall worse outcomes. The lack of antidote is particularly troubling in the setting of ICB, possibly the most feared complication of anticoagulant treatment. The evidence addressing the severity of intracranial hemorrhages in patients using NOACs, however, is limited. In a secondary analysis of the 150 intracranial hemorrhages occurring in the RE-LY trial, mortality was similar in patients randomized to receive dabigatran or warfarin.[7] Likewise, receiving rivaroxaban or warfarin was not associated with mortality in the 172 intracranial hemorrhages identified in the ROCKET-AF trial.[8] These results, however, derive from a randomized trial and might not be directly applicable to less controlled environments in real-world populations. To date, data from other settings has been limited to case reports and several small case series of patients receiving NOACs, without direct comparison with warfarin-treated patients.[9]

To provide additional evidence that could inform prescribing decisions for clinicians and patients, we studied the in-hospital mortality of AF patients with intracranial hemorrhages that were receiving dabigatran or warfarin in a real-world population, using a large healthcare utilization database.

METHODS

Study population

We used claims data from the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database

(Truven Health Analytics Inc., Ann Arbor, MI) for the period January 1, 2009 to December 31, 2012 (the FDA approved dabigatran for stroke prophylaxis in AF in October 2010). The MarketScan Commercial Database includes health insurance claims spanning all levels of care as well as enrollment data from large employers and health plans across the US providing private healthcare coverage for employees, their spouses, and dependents. The MarketScan Medicare Supplemental Database includes claims from individuals and their dependents with Medicare supplemental coverage. Both databases link medical and outpatient prescription drug claims and encounter data with patient enrollment data to provide individual-specific clinical utilization, expenditure, and outcomes information across inpatient and outpatient services, and outpatient pharmacy services.

Our analysis was restricted to individuals enrolled in plans with available outpatient pharmaceutical data, admitted to a hospital with a primary diagnosis of ICB, with at least six months of continuous enrolment before the ICB hospitalization, and with a prior history of AF. We defined ICB as the first hospitalization with any of the following International Classification of Disease 9th Edition Clinical Modification (ICD-9-CM) codes as the primary diagnosis: 430.x, 431.x, 432.x, 852.x, and 853.x. Validation studies have demonstrated these codes to have high positive predictive value for intracranial hemorrhage.[10] The admission date for this hospitalization was considered the index date. A history of AF was defined as at least one inpatient claim or two outpatient claims at least one week apart with the ICD-9-CM codes 427.31 or 427.32 in any position before the index date.[11] Patients with AF enrolled in the MarketScan Medicare Supplemental Database have similar demographic characteristics to AF patients in the general fee-for-service Medicare population.[12, 13]

All patient information was Health Insurance Portability and Accountability Act–compliant, de-identified, commercially available secondary data and therefore the Institutional Review Board at the University of Minnesota deemed this analysis exempt from review.

Anticoagulant use

In both MarketScan databases, each individual outpatient pharmaceutical claim includes information on National Drug Code, date of service, and days supplied, among other variables. We identified all prescriptions for dabigatran and warfarin occurring before the index date (ICB hospitalization). Patients were considered current users of a specific anticoagulant at the index date if the ICB hospitalization occurred during an active prescription for oral anticoagulation. In a sensitivity analysis, we added to the current users those with an oral anticoagulant prescription ending in the 7-day period before the index date (ICB hospitalization). Only 12 ICB events (3 deaths) occurred in rivaroxaban users and therefore they were excluded from the analysis.

Outcome and other covariates

The outcome of interest, in-hospital mortality, was directly obtained from the inpatient claims. Other covariates were ascertained from inpatient and outpatient claims before the index date using ICD-9-CM codes and previously published algorithms.[14, 15] These covariates comprised those included in scores for the prediction of stroke ($CHADS_2$,

CHA_2DS_2-VASc) and hemorrhagic complications in AF patients (ATRIA, $HEMORR_2HAGES$, HAS-BLED) (see Supplemental Tables I and II for score definitions, diagnostic codes, and bibliographic references). Similarly, we assessed the presence of prescription for the following medication groups before the index date: antiplatelets, digoxin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, type I and III antiarrhythmics, beta-blockers, calcium channel blockers, lipid lowering medications, and diuretics.

Statistical analysis

The primary analysis included current users of oral anticoagulants at the index date. We estimated the association between type of oral anticoagulant and in-hospital mortality using relative risk (log-binomial) regression (PROC GENMOD in the SAS software), comparing current users of dabigatran to current warfarin users.

In all analyses, an initial model was adjusted for age, sex, and hemorrhage subtype (intracerebral hemorrhage, subarachnoid hemorrhage, unspecified intracranial hemorrhage, non-traumatic subdural hemorrhage, traumatic subdural hemorrhage, unspecified traumatic intracranial hemorrhage). A second model additionally adjusted for CHA_2DS_2-VASc and ATRIA bleeding scores. We adjusted for these scores because, among the considered stroke and bleeding predictive models in AF, they were the strongest predictors of in-hospital mortality in our study sample. Third, we ran a model adjusted for age, sex, hemorrhage type, and deciles of propensity score (as a categorical variable). Propensity scores were calculated from a logistic regression model with current use of warfarin (vs dabigatran) as the dependent variable, and all variables in table 1 as the independent variables. A final analysis was performed in propensity score-matched warfarin and dabigatran users. Each dabigatran user was matched with up to three warfarin current users by index date (60 days caliper), age at index date (3 years caliper), sex, and propensity score (0.03 caliper).[16] Analyses stratified by sex, age (below or above median), history of kidney disease, and ATRIA bleeding score (below or above median) were also conducted. Interactions were tested including multiplicative terms in the models. We conducted two additional sensitivity analyses. First, we included patients who had been using their current anticoagulant for 6 months or less and, in a different model, for 1 year or less. Second, we restricted the analysis to non-traumatic intracranial bleeds.

RESULTS

We identified 2391 hospitalizations with a primary diagnosis of ICB among AF patients who were current users of one anticoagulant at the time of the event (2290 were on warfarin, 101 on dabigatran) (Supplemental Figure I). Four additional events were excluded due to being current users of more than 1 anticoagulant. Patient characteristics by type of anticoagulant are presented in Table 1. Overall, no statistically significant differences in mean age, sex, or mean risk of ischemic stroke by the $CHADS_2$ or CHA_2DS_2-VASc scores were found across groups. According to all bleeding scores, risk of hemorrhage was higher in dabigatran users compared to warfarin users. Dabigatran users had a higher prevalence of prior history of gastrointestinal bleeding.

Among the 2391 ICB events, 531 in-hospital deaths occurred (22% mortality). In-hospital mortality was similar in warfarin (22%) and dabigatran users (20%). Adjusting for age and sex, in-hospital mortality was similar in both groups (RR 0.89, 95%CI 0.60, 1.33). Similarly, in multivariable and propensity score-adjusted or matched models, current use of dabigatran compared to current use of warfarin was not associated with mortality (Table 2). Results were comparable in sensitivity analyses adding to the current users those with their most recent oral anticoagulant prescription ending in the 7 days before the ICB hospitalization date (which added 187 cases; Supplemental Table III), restricting the analysis to patients with less than 6 months or 1 year on their current anticoagulant regime (Supplemental Table IV), and including only non-traumatic hemorrhages (Supplemental Table V). Hemorrhage subtype analyses were limited due to small numbers and imprecise estimates but suggested lower mortality associated with dabigatran use in subdural hemorrhage and higher mortality in intracerebral hemorrhage, compared to warfarin use (Table 3).

In stratified analysis (Table 4), associations between anticoagulant type and mortality were similar in younger and older patients, with or without kidney disease history, and with low or high bleeding risk assessed by the ATRIA score. A significant interaction with sex was observed (p=0.03): among men, mortality was lower in dabigatran users compared to warfarin users (RR 0.54, 95%CI 0.25, 1.14), while the opposite pattern was observed for women (RR 1.49, 95%CI 0.96, 2.29).

DISCUSSION

In this retrospective analysis of healthcare utilization data, in-hospital mortality in AF patients using oral anticoagulants hospitalized with ICB was similar in warfarin and dabigatran users. The lack of association is unlikely to be due to confounding by indication given the extensive adjustment for clinical covariates. Our results do not support the notion that, in patients with ICB, use of dabigatran is associated with worse prognosis, assessed as in-hospital mortality, relative to use of warfarin.

The present analysis is based on a relatively small number of ICB events in current dabigatran users (101 cases with 20 deaths), but is consistent with reports from the RE-LY trial, where mortality in patients suffering an ICB did not differ by treatment allocation. In the RE-LY trial, mortality was 38% and 36% in patients with ICB assigned to dabigatran and warfarin, respectively.[7] Of note, mortality in the RE-LY trial was higher than that reported in the present analysis because of differences in mortality follow-up (in-hospital mortality in our analysis vs. extended follow-up in RE-LY) and because of a higher proportion of intracerebral hemorrhages, which have worse prognosis, among all ICB events in the RE-LY trial population. No other studies have examined directly the outcomes and prognosis of intracranial hemorrhages in dabigatran versus warfarin users in real-world populations, outside the more controlled setting of clinical trials. Case reports and several small cases series of intracranial hemorrhages in dabigatran users have been published, mostly focusing on their clinical management, but they only provide limited evidence of the comparative effectiveness of dabigatran and warfarin.[9]

Our findings run counter to the belief that patients receiving dabigatran who experience severe bleeding may have worse outcomes than warfarin users given the lack of approved reversal agents for the former.[6] Several reasons could explain our results. First, in the setting of an ICB event, even the theoretical availability of reversal agents for vitamin K antagonists might not be enough to prevent the poor outcome of these episodes if their administration is delayed, leading to similar mortality rates. In addition, the half-life of dabigatran is shorter than that of warfarin, potentially reducing their impact in the setting of bleeding.[17] Finally, evidence from animal models indicates that intracerebral hemorrhage volume may be lower and that active bleeding may terminate earlier in dabigatran-treated than warfarin-treated mice.[18–20]

The lack of association between type of oral anticoagulant and in-hospital mortality was observed across subgroups defined by age, history of kidney disease, or bleeding risk. However, we found evidence that sex modified the mortality risk associated with dabigatran versus warfarin. Specifically, compared to warfarin use, dabigatran use was associated with higher mortality in women but lower in men. No obvious explanation can be provided for this difference. It is possible that metabolism of dabigatran may differ by sex; alternately this observation could be also due to chance. Replication in independent samples is required.

Two additional considerations should be taken into account when interpreting our findings. First, if a particular anticoagulant is associated with severity of bleeding leading to higher out-of-hospital mortality, we would underestimate mortality in that group. Unfortunately, our data do not include information to test this hypothesis. Second, even though all patients included in our analysis were current users of oral anticoagulation, it is possible that warfarin users have been using their medication for a longer time period than dabigatran users, survived other complications, and therefore might be a selected, more resilient group than the dabigatran users. As we have shown, however, characteristics of warfarin and dabigatran users were similar. Also, results did not change in analyses adjusting for time since first anticoagulant prescription.

Strengths of our study include the relatively large number of ICB events and the availability of an extensive array of clinical information for confounding adjustment. Some limitations need to be highlighted, however. Though previous studies have shown high specificity of claims for the diagnosis of intracranial hemorrhage,[10] we did not have access to medical charts to validate the diagnosis. Similarly, we did not have information on bleeding-related prognostic variables (e.g. bleeding location or size), or in the clinical management of these patients, including hemostatic approaches, which could have been different in warfarin and dabigatran users. Despite our efforts to capture and adjust for relevant potential confounding factors associated with mortality, residual confounding may have masked true differences in mortality between anticoagulant groups. In addition, our sample size may have been insufficient to identify relatively small differences in mortality between groups and to estimate precisely the associations within specific ICB subtypes (for instance, we only identified 25 intracerebral hemorrhages among dabigatran users). Last of all, our outcome was in-hospital mortality and we did not have the possibility of assessing longer term mortality and functional outcomes.

In conclusion, despite the lack of approved reversal agents, in-hospital mortality among AF patients admitted with an ICB in a real-world setting in the United States was comparable in warfarin and dabigatran users. Our results may help clinicians and patients with AF make informed decisions, adequately balancing risk and benefits, when choosing an oral anticoagulant for the prevention of thromboembolic complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of atrial fibrillation patients at the time of index intracranial hemorrhage by anticoagulant use, MarketScan 2009–2012

	Warfarin	Dabigatran	P-value*
N	2290	101	
Age, years	76.1±10.3	75.1±8.8	0.30
Range	19–98	48–94	
Women	44.5	46.5	0.68
$CHADS_2$	3.1±1.4	3.1±1.4	0.75
CHA_2DS_2-VASc	4.5±1.7	4.6±1.9	0.74
ATRIA	4.0±2.4	4.3±2.5	0.32
HAS-BLED†	2.8±1.2	3.2±1.1	0.001
$HEMORR_2HAGES$‡	3.6±1.8	4.0±1.8	0.01
History of:			
Heart failure	50.6	42.6	0.12
Diabetes	36.6	32.7	0.43
Myocardial infarction	12.7	9.9	0.41
Hypertension	85.9	96.0	0.004
Kidney disease	19.2	20.8	0.69
Liver disease	5.9	9.9	0.10
Ischemic stroke	35.4	43.6	0.09
Gastrointestinal bleeding	12.6	25.7	<0.001
Previous intracranial bleeding	2.7	5.0	0.20
Other bleeding	24.1	24.8	0.88
Excessive alcohol consumption	2.1	5.0	0.07
Anemia	32.0	38.6	0.16
Coagulopathy	26.7	26.7	0.98
Cancer	21.0	30.7	0.02
Previous use of:			
Antiplatelet	13.3	15.8	0.47
Digoxin	32.1	29.7	0.62
ACE inhibitors	42.7	39.6	0.54
Angiotensin receptor blockers	26.7	33.7	0.13
Class I and III antiarrhythmics	18.0	28.7	0.007
Beta blocker	75.9	82.2	0.15
Calcium channel blocker	42.9	48.5	0.26
Lipid lowering medications	67.3	72.3	0.29
Diuretics	63.2	62.4	0.87

Values correspond to means ± standard deviation or percentage

[*] P-values from t-test for continuous variables or chi-square for categorical variables testing equality of means or proportions

[†] Calculation of HAS-BLED score excludes 'INR labile' variable

[‡] Calculation of HEMORR$_2$HAGES score excludes 'Excessive fall risk' variable

Table 2

Risk ratios (95% confidence intervals) of in-hospital death in current users of dabigatran compared to current users of warfarin admitted with intracranial bleeding, MarketScan databases, 2009–2012

	Warfarin	Dabigatran
N	2290	101
In-hospital deaths [n(%)]	511 (22.3)	20 (19.8)
Model 1	1 (ref.)	0.96 (0.65, 1.42)
Model 2	1 (ref.)	0.94 (0.64, 1.39)
Model 3	1 (ref.)	0.97 (0.65, 1.43)
Model 4	1 (ref.)	0.88 (0.56, 1.36)

Model 1: Adjusted for age, sex, and hemorrhage subtype

Model 2: Model 1, additionally adjusted for CHA_2DS_2-VASc score and ATRIA bleeding score

Model 3: Adjusted for age, sex, hemorrhage subtype, and propensity score deciles

Model 4: Propensity score-matched analysis. Analysis included 239 warfarin users (59 deaths) and 87 dabigatran users (18 deaths)

Table 3

Risk ratios (95% confidence intervals) of in-hospital death in current users of dabigatran compared to current users of warfarin admitted with intracranial bleeding, by bleeding subtype, MarketScan databases, 2009–2012

	Warfarin	**Dabigatran**
Intracerebral hemorrhage		
N	723	25
In-hospital deaths (% mortality)	244 (33.8)	11 (44.0)
Model 1	1 (ref.)	1.30 (0.83, 2.04)
Model 2	1 (ref.)	1.28 (0.82, 2.01)
Model 3	1 (ref.)	1.28 (0.82, 1.99)
Model 4	1 (ref.)	1.00 (0.59, 1.69)
Subdural		
N	1178	55
In-hospital deaths (% mortality)	179 (15.2)	4 (7.3)
Model 1	1 (ref.)	0.50 (0.19, 1.30)
Model 2	1 (ref.)	0.50 (0.19, 1.30)
Model 3	1 (ref.)	0.47 (0.18, 1.23)
Model 4	1 (ref.)	0.49 (0.18, 1.34)
Subarachnoid / intracranial bleeding NOS		
N	389	21
In-hospital deaths (% mortality)	88 (22.6)	5 (23.8)
Model 1	1 (ref.)	1.01 (0.46, 2.23)
Model 2	1 (ref.)	0.95 (0.43, 2.08)
Model 3	1 (ref.)	0.99 (0.44, 2.20)
Model 4	1 (ref.)	1.13 (0.36, 3.50)

Model 1: Adjusted for age and sex

Model 2: Model 1, additionally adjusted for CHA_2DS_2-VASc score and ATRIA bleeding score

Model 3: Adjusted for age, sex, and propensity score deciles

Model 4: Propensity score matched analysis adjusting for age and sex.

Table 4

Risk ratios (95% confidence intervals) of in-hospital mortality in dabigatran users versus warfarin users across selected subgroups. Models adjusted for age, sex (where appropriate), hemorrhage subtype, and propensity score deciles.

	Warfarin		Dabigatran		RR (95%CI)
	N.	In-hospital deaths [n(%)]	N.	In-hospital deaths [n(%)]	
Men	1272	305 (24.0)	54	6 (11.1)	0.53 (0.25, 1.14)
Women	1018	206 (20.2)	47	14 (29.8)	1.49 (0.96, 2.29)
Interaction p-value					0.03
Age ≤77	1071	224 (20.9)	60	10 (16.7)	0.92 (0.51, 1.64)
Age >77	1219	287 (23.5)	41	10 (24.4)	1.05 (0.61, 1.81)
Interaction p-value					0.74
Previous kidney disease	439	120 (27.3)	21	6 (28.6)	1.14 (0.56, 2.29)
No kidney disease	1851	391 (21.1)	80	14 (17.5)	0.93 (0.57, 1.50)
Interaction p-value					0.95
ATRIA bleeding score ≤4	1498	320 (21.4)	63	12 (19.1)	0.96 (0.57, 1.59)
ATRIA bleeding score >4	792	191 (24.1)	38	8 (21.1)	1.06 (0.57, 1.97)
Interaction p-value					0.83

CI: Confidence interval; RR: Risk ratio.