Anticoagulation Use and Clinical Outcomes After Major Bleeding on Dabigatran or Warfarin in Atrial Fibrillation

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Background and Purpose—Little is known about the clinical outcomes associated with posthemorrhage anticoagulation resumption for atrial fibrillation. This study had 2 objectives: first, to evaluate anticoagulation use after a first major bleed on warfarin or dabigatran and, second, to compare effectiveness and safety outcomes between patients discontinuing anticoagulation after a major bleed and patients restarting warfarin or dabigatran.

Methods—Using 2010 to 2012 Medicare Part D data, we identified atrial fibrillation patients who experienced a major bleeding event while using warfarin (n=1135) or dabigatran (n=404) and categorized them by their posthemorrhage use of anticoagulation. We followed them until an ischemic stroke, recurrent hemorrhage, or death through December 31, 2012. We constructed logistic regression models to evaluate factors affecting anticoagulation resumption and Cox proportional hazard models to compare the combined risk of ischemic stroke and all-cause mortality and the risk of recurrent bleeding between treatment groups.

Results—Resumption of anticoagulation with warfarin (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.59–0.97) or dabigatran (HR 0.66; 95% CI 0.44–0.99) was associated with lower combined risk of ischemic stroke and all-cause mortality than anticoagulation discontinuation. The incidence of recurrent major bleeding was higher for patients prescribed warfarin after the event than for those prescribed dabigatran (HR 2.31; 95% CI 1.19–4.76) or whose anticoagulation ceased (HR 1.56; 95% CI 1.10–2.22), but did not differ between patients restarting dabigatran and those discontinuing anticoagulation (HR 0.65; 95% CI 0.32–1.33).

Conclusions—Dabigatran was associated with a superior benefit/risk ratio than warfarin and anticoagulation discontinuation in the treatment of atrial fibrillation patients who have survived a major bleed. (Stroke. 2017;48:159-166. DOI: 10.1161/STROKEAHA.116.015150.)

Key Words: anticoagulants ■ atrial fibrillation ■ dabigatran ■ hemorrhage ■ stroke

Anticoagulation therapy reduces the risk of stroke associated with atrial fibrillation (AF) by ≈60%.1 Anticoagulation, however, is not free of risks, being an important determinant of bleeding. The optimal management of AF patients who have experienced a major bleeding complication is uncertain because there are competing risks from both the resumption and the discontinuation of anticoagulation: although patients experiencing a major bleed are at increased risk of recurrent bleeding events, they are also at a high risk of thromboembolic events, if anticoagulation is not reinitiated.3–6 The uncertainty surrounding decisions about the posthemorrhage use of anticoagulation is relevant from the clinical perspective, particularly, because patients who are at highest risk of bleeding are also at highest risk of stroke.5,7

Previous studies that examined the clinical outcomes of patients who resumed versus those who discontinued anticoagulation after a major bleed found that resumption of anticoagulation was associated with lower risk of thromboembolic events, but higher risk of bleeding.3–6 Nevertheless, in comparing clinical outcomes between these 2 groups of patients, these studies did not account for the type of anticoagulation agent used and used data that preceded the market entry of the non-vitamin K antagonist oral anticoagulants.5–6 With no requirement for routine coagulation assay monitoring, and with a lower risk of intracranial bleeding, the therapeutic management and bleeding profile of the non-vitamin K antagonist oral anticoagulants are considerably different from those of warfarin.6 Consequently, the clinical outcomes associated with the resumption of anticoagulation after a major bleeding event may differ between patients reinitiating warfarin therapy and those reinitiating non-vitamin K antagonist oral anticoagulants. Therefore, it is important to separately evaluate the risks of stroke and recurrent bleeding among patients who resume anticoagulation with warfarin.
those who reinitiate anticoagulation with the non-vitamin K antagonist oral anticoagulants, and those who discontinue all anticoagulation.

Therefore, our present analysis had 2 objectives: first, to evaluate the patterns of oral anticoagulation use after a major bleeding event on dabigatran or warfarin and to identify predictors for posthemorrhage resumption of oral anticoagulation and, second, to compare the combined risk of ischemic stroke and all-cause mortality and the risk of recurrent bleeding events between patients who resume anticoagulation with warfarin or dabigatran versus those whose anticoagulation is ceased.

Methods

Data Source and Study Population

We obtained 2010 to 2012 data for a 5% random sample of Medicare beneficiaries from the Centers for Medicare and Medicaid Services. First, we identified all patients who had a diagnosis of AF and filled a prescription for dabigatran or warfarin between October 19, 2010 (date of dabigatran approval), and June 30, 2012 (Figure 1). To make sure that the warfarin group was representative of patients initiating warfarin and, hence, comparable to the dabigatran group, we excluded all individuals who had filled a prescription for warfarin during the 6 months before October 19, 2010. We followed 10059 dabigatran users and 79714 warfarin users from the date of the first prescription of dabigatran or warfarin after October 19, 2010, to December 31, 2012, until the first of the following events: major bleeding, discontinuation of treatment, defined as a gap in treatment for over 60 days, switch of anticoagulant, or death. Second, we selected those who experienced a major bleeding event that required hospitalization (index major hemorrhage) and identified those who were discharged alive. Third, we collected their prescriptions for oral anticoagulant agents filled after the date of the index major hemorrhage and categorized them according to the oral anticoagulation agent used. Patients who filled a prescription for dabigatran or warfarin after the bleeding event were followed from the date of the first anticoagulant prescription after index major hemorrhage (posthemorrhage follow-up start date) to December 31, 2012, or until the occurrence of a stroke, a recurrent bleeding event, or death. To set the posthemorrhage follow-up start date for patients who never filled a prescription for an oral anticoagulant agent after the index major hemorrhage, we performed frequency matching. Further details on frequency matching can be found in Methods in the online-only Data Supplement. Patients who switched to rivaroxaban were not included in the study because of the small sample size of this treatment group (n=8 in the dabigatran cohort and n=9 in the warfarin cohort). This study was approved by the Institutional Review Board at the University of Pittsburgh as exempt.

Outcomes

Effectiveness outcomes included ischemic stroke, all-cause mortality, and the composite of ischemic stroke and all-cause mortality. Ischemic stroke was defined as having one inpatient, emergency room, or outpatient claim with primary or secondary International Classification of Diseases, Ninth Revision codes 433, 434, or 436. Safety outcomes included recurrent major bleeding and any recurrent bleeding event (definitions in Methods in the online-only Data Supplement).

Covariates

We evaluated how different demographic factors, clinical characteristics, anatomic location, and severity of the index major hemorrhage affected the posthemorrhage use of oral anticoagulation. All covariates were measured at the time of the index major hemorrhage. Demographic characteristics included age, sex, race, and eligibility for Medicaid coverage. Clinical covariates included CHA$_2$DS$_2$-VASc score, HAS-BLED score, and several other Centers for Medicare and Medicaid Services priority comorbidities. (CHA$_2$DS$_2$-VASc score measures of the risk of stroke in patients with AF. To calculate CHA$_2$DS$_2$-VASc, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points. HAS-BLED score is a prediction score of the risk of major bleeding for patients with AF on anticoagulation. In calculating the HAS-BLED score, age of 65 or greater, labile INR, renal disease, liver disease, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs, and a history of hypertension, stroke, major bleeding and alcohol or drug use are all assigned one point. Because Medicare claims data do not contain information on the international normalized ratio, we calculated the HAS-BLED score as the sum of all previous factors, except labile international normalized ratio. We categorized the anatomic location of the index major hemorrhage into 4 groups: intracranial bleeding, gastrointestinal hemorrhage, genitourinary hemorrhage, and other bleeding events, which included hemoperitoneum, epistaxis, hemoptyis, hemarthrosis, conjunctival, and vaginal hemorrhage and not-otherwise-specified hemorrhage. Measures of the severity of the index major hemorrhage included length of inpatient stay, intensive care unit admission, and blood transfusion therapy and whether the patients underwent corrective procedures in the same anatomic area of the bleeding. The definitions of covariates can be found in Methods in the online-only Data Supplement.

Statistical Analysis

We compared patient characteristics of 3 posthemorrhage treatment groups in each cohort at the time of index major hemorrhage using \textit{t} tests, Fisher’s exact tests, and analysis of variance, as appropriate. To predict the probability of restarting the same anticoagulation agent used before the index bleeding event or switching to another agent as opposed to discontinuing oral anticoagulation, we constructed a multinomial logistic regression model with generalized logit link function, where the outcome variable was the posthemorrhage treatment group, and covariates included all variables listed in the Covariates section.

Kaplan–Meier time-to-event curves were constructed to compare the cumulative incidence rates of effectiveness and safety outcomes at 3 months, 6 months, and 1 year posthemorrhage follow-up among the posthemorrhage treatment groups. To further control for potential confounders in comparing effectiveness and safety outcomes, we constructed Cox Proportional Hazard models. Cox models built to compare effectiveness outcomes controlled for age, CHA$_2$DS$_2$-VASc score, HAS-BLED score, and an indicator variable for the location of the index major hemorrhage (1 if intracranial and 0 otherwise). Cox models built to compare safety outcomes controlled for CHA$_2$DS$_2$-VASc, HAS-BLED score, an indicator variable for the location of the index major hemorrhage (1 if intracranial and 0 otherwise), and the measures of the severity of the index bleeding event, as detailed earlier. For all time-to-event analyses, time 0 was the posthemorrhage follow-up start date (defined in the Data Source and Study Population section). The time at risk was censored at the end of the study period (December 31, 2012) or at the time of death, except for the Kaplan–Meier and Cox models, whose outcome included mortality. In those analyses, the time at risk was only censored at the end of the study period. All of these analyses were performed separately for the dabigatran and the warfarin cohorts. In a secondary analysis, we grouped patients from the warfarin and dabigatran cohorts according to the treatment used after the index major hemorrhage and compared effectiveness and safety outcomes using Cox models in a similar manner, as described earlier. All analyses were conducted with statistical software SAS 9.4 (Cary, NC).

Sensitivity Analysis

Posthemorrhage clinical outcomes of patients who experienced an intracranial bleeding are likely to differ from those who bled on...
other anatomic locations. To examine how this may have affected our results for the comparative risk of posthemorrhage clinical outcomes, we repeated our analysis after excluding patients who experienced an intracranial bleeding.

**Results**

**Posthemorrhage Anticoagulation Use and Patient Characteristics**

The proportion of patients who reinitiated anticoagulation after the index major hemorrhage was similar between the warfarin and dabigatran cohorts (49% for dabigatran and 47% for warfarin; \( P \) value = 0.497). However, dabigatran users were more likely to switch to warfarin after the bleeding event than warfarin users were to switch to dabigatran (17% versus 2%; \( P \) value < 0.001). In addition, resumption of the same oral anticoagulation agent used before the index major hemorrhage was more common in the warfarin cohort than in the dabigatran cohort (41% versus 28%, with \( P \) value < 0.001). In the dabigatran cohort, the mean time from index bleeding to anticoagulation resumption was 45 days for patients who resumed dabigatran and 73 days for those who switched to warfarin (\( P \) value = 0.005). In the warfarin cohort, the average time from index bleeding to anticoagulation resumption was 60 days for patients who resumed warfarin and 70 days for those who switched to dabigatran (\( P \) value = 0.501). The average follow-up time for each group and cohort can be found in Table II in the online-only Data Supplement.

Table shows how patient characteristics at baseline compare among posthemorrhage treatment groups. Older patients were more likely to discontinue anticoagulation after the index hemorrhage in both cohorts. Specifically, the odds of resuming dabigatran or switching to warfarin compared with discontinuing anticoagulation decreased by 24% (95% confidence interval [CI] 9% to 37%) and 28% (95% CI 10% to 42%) for every 5 years increase in age, respectively (Figure 2). In the warfarin cohort, patients who experienced an intracranial bleeding, were admitted to the intensive care unit, or received a blood transfusion were more likely to cease anticoagulation (Figure 3).

**Ischemic Stroke**

Before adjustment, there was no difference in the risk of stroke among treatment groups in the 2 cohorts: the cumulative incidence of ischemic stroke at 1 year was 0.20 (95% CI 0.12–0.29) for dabigatran users resuming dabigatran, 0.15 (95% CI 0.08–0.21) for dabigatran users who discontinued anticoagulation, 0.21 (95% CI 0.10–0.32) for dabigatran users switching to warfarin, 0.14 (95% CI 0.11–0.18) for warfarin users resuming warfarin, 0.14 (95% CI 0.11–0.18) for warfarin users resuming warfarin, 0.14 (95% CI 0.11–0.18) for warfarin users who discontinued anticoagulation, and 0.25 (95% CI 0.06–0.44) for warfarin users switching to dabigatran (Table III in the online-only Data Supplement). After adjustment for potential confounders, the risk of ischemic stroke did not differ between patients who resumed dabigatran (hazard ratio [HR] 1.29; 95% CI 0.69–2.43) or switched to warfarin (HR 1.29; 95% CI 0.63–2.65) and those who did not reinitiate
anticoagulation (Figure 4). In the warfarin cohort, similarly, the risk of ischemic stroke did not differ among treatment groups (HR 1.26; 95% CI 0.88–1.80 for resumption of warfarin versus discontinuation of anticoagulation and HR 1.81; 95% CI 0.72–4.53 for switching to dabigatran versus discontinuation of anticoagulation). When the 2 cohorts were analyzed simultaneously based on the treatment received after the index hemorrhage, once again, there was no difference in the risk of ischemic stroke among posthemorrhage treatment groups.

Ischemic Stroke and All-Cause Mortality
The cumulative incidence of all-cause mortality at 1 year was higher for patients who discontinued anticoagulation (0.13; 95% CI 0.08–0.18 for patients on the dabigatran cohort and 0.15; 95% CI 0.12–0.18 for patients on the warfarin cohort) than for those who restarted anticoagulation (0.02; 95% CI 0.00–0.04 for dabigatran users resuming dabigatran and 0.07; 95% CI 0.04–0.09 for warfarin users resuming warfarin; Table III in the online-only Data Supplement). After adjustment for potential confounders, the risk of all-cause mortality was lower for patients on the dabigatran cohort who resumed dabigatran (HR 0.13; 95% CI 0.03–0.58) or switched to warfarin (HR 0.21; 95% CI 0.05–0.91) than for those who did not reinitiate anticoagulation (Figure 4). In the warfarin cohort, resumption of warfarin was associated with lower composite risk of ischemic stroke and all-cause mortality (HR 0.75; 95% CI 0.57–0.98) and lower risk of all-cause mortality (HR 0.35; 95% CI 0.23–0.55) than discontinuation of anticoagulation.

When the 2 cohorts were analyzed simultaneously based on the treatment received after the index hemorrhage, we found that the composite risk of ischemic stroke and all-cause mortality was lower for patients who were prescribed warfarin
Recurrent Bleeding

There were no differences in the unadjusted risk of bleeding events among posthemorrhage treatment groups in the dabigatran cohort (Table III in the online-only Data Supplement): the cumulative incidence of major recurrent bleeding at 1 year was 0.07 (95% CI 0.02–0.11) for dabigatran users who resumed dabigatran, 0.09 (95% CI 0.04–0.14) for those who continued anticoagulation, and 0.09 (95% CI 0.01–0.17) for those switching to warfarin. However, in the warfarin cohort, the unadjusted risk of recurrent major bleeding at 1 year was lower for patients who discontinued anticoagulation (0.10; 95% CI 0.07–0.13) than for those who restarted warfarin after the index hemorrhage (0.17; 95% CI 0.13–0.21). These unadjusted results were consistent with the findings of the adjusted analysis: the risks of major and any bleeding events were similar for 3 treatment groups in the dabigatran cohort (Figure 4). In the warfarin cohort, however, the risk of major bleeding was higher for patients resuming warfarin compared with those discontinuing all anticoagulation (HR 1.60; 95% CI 1.09–2.36).

When the 2 cohorts were combined based on the treatment received after the index hemorrhage, we found that the risk of major hemorrhage was higher for patients who were prescribed warfarin than for those who were prescribed dabigatran or who discontinued anticoagulation therapy. Specifically, the HR of recurrent major bleeding was 0.42 (95% CI 0.21–0.84) for dabigatran compared with warfarin and 1.59 (95% CI 1.10–2.22) for warfarin compared with anticoagulation discontinuation. The risk of bleeding did not differ between patients who were prescribed dabigatran after the index hemorrhage and those whose anticoagulation was discontinued (HR 0.65; 95% CI 0.32–1.33).

Table IV in the online-only Data Supplement shows the anatomic location of the recurrent bleeding events, stratified by the anatomic location of the index hemorrhage. The highest-est incidence of recurrent intracranial hemorrhage was for patients in the warfarin cohort who resumed warfarin (25%).

Sensitivity Analyses

Our results for the HRs of posthemorrhage clinical outcomes were robust to the exclusion of patients who experienced an intracranial bleeding event (Table V in the online-only Data Supplement).
To the best of our knowledge, our study is the first real-world analysis comparing clinical outcomes after a major hemorrhage among patients who reinitiated anticoagulation therapy with dabigatran or warfarin and those who never resumed anticoagulation. Our study has 4 main findings: first, we found that posthemorrhage use of warfarin was more common than that of dabigatran in 2010 to 2012. Second, we observed that the CHA2DS2-VASc and HAS-BLED scores did not affect the likelihood of reinitiating anticoagulation after a major bleeding event. In contrast, age, anatomic location, and severity of the index bleeding event were the most important determinants of resuming anticoagulation. Third, compared with discontinuation of all anticoagulation, resumption of anticoagulation therapy with either dabigatran or warfarin was associated with higher rates of survival and stroke-free survival. Fourth, the risk of recurrent major hemorrhage was higher for patients who were prescribed warfarin after a first major bleeding compared with those who were prescribed dabigatran or those whose anticoagulation was never reinitiated.

Our estimate for the HR of all-cause mortality for patients who reinitiated warfarin compared with those who discontinued anticoagulation (HR 0.35; 95% CI 0.23–0.53) is similar to the one reported by Staerk et al7 (HR 0.39; 95% CI 0.34–0.46). Regardless of the consistency of these findings, the association of anticoagulation resumption with increased survival may be subject to residual confounding because patients who discontinued anticoagulation had higher burden of disease than those who resumed anticoagulation. In our analyses, we controlled for CHA2DS2-VASc, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points.7 HAS-BLED score is a prediction score of the risk of major bleeding for patients with AF on anticoagulation. In calculating the HAS-BLED score, age of 65 or greater, labile INR, renal disease, liver disease, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs, and a history of hypertension, stroke, major bleeding and alcohol or drug use are all assigned one point.7 CMS indicates Centers for Medicare and Medicaid Services; GI, gastrointestinal; IC, intracranial; and INR, international normalized ratio.

Discussion

To the best of our knowledge, our study is the first real-world analysis comparing clinical outcomes after a major hemorrhage among patients who reinitiated anticoagulation therapy with dabigatran or warfarin and those who never resumed anticoagulation. Our study has 4 main findings: first, we found that posthemorrhage use of warfarin was more common than that of dabigatran in 2010 to 2012. Second, we observed that the CHA2DS2-VASc and HAS-BLED scores did not affect the likelihood of reinitiating anticoagulation after a major bleeding event. In contrast, age, anatomic location, and severity of the index bleeding event were the most important determinants of resuming anticoagulation. Third, compared with discontinuation of all anticoagulation, resumption of anticoagulation therapy with either dabigatran or warfarin was associated with higher rates of survival and stroke-free survival. Fourth, the risk of recurrent major hemorrhage was higher for patients who were prescribed warfarin after a first major bleeding compared with those who were prescribed dabigatran or those whose anticoagulation was never reinitiated.

Figure 3. Odds ratio of posthemorrhage anticoagulation use for the warfarin cohort. Results from a multinomial logistic regression model. The odds ratio for switching to dabigatran as opposed to interrupting anticoagulation for patients of other race compared with white patients could not be estimated because none of the patients belonging to other racial minorities switched to dabigatran after the index bleeding event. CHA2DS2-VASc score measures of the risk of stroke in patients with AF. To calculate CHA2DS2-VASc, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points.7 HAS-BLED score is a prediction score of the risk of major bleeding for patients with AF on anticoagulation. In calculating the HAS-BLED score, age of 65 or greater, labile INR, renal disease, liver disease, use of antplatelet agents or of nonsteroidal anti-inflammatory drugs, and a history of hypertension, stroke, major bleeding and alcohol or drug use are all assigned one point.7 CMS indicates Centers for Medicare and Medicaid Services; GI, gastrointestinal; IC, intracranial; and INR, international normalized ratio.

Study Implications

Our study contributes significantly to the existing literature because, as opposed to previous work, it stratified treatment groups into 2 cohorts according to the type of anticoagulation agent used after the index bleeding event. In doing so, we demonstrate the benefit of the use of anticoagulation therapy after a major bleeding event. More specifically, we found that the resumption of anticoagulation therapy after a major hemorrhage was associated with a lower incidence of stroke and all-cause mortality than anticoagulation discontinuation. In contrast, less than half of the patients who survived a major hemorrhage in 2010 to 2012 restarted anticoagulation,
which likely represents prescribers’ aversion to the perceived high risk of recurrent hemorrhage. However, in our study, we found that the risk of recurrent major bleeding was lower than the risk of ischemic stroke for all treatment groups and that the risk of recurrent major bleeding did not differ between treatment groups in the dabigatran cohort. These results should encourage clinicians to resume anticoagulation among patients who survived a major bleeding event. When comparing outcomes associated with the resumption of warfarin and dabigatran, we found that the benefit/risk ratio of posthemorrhage dabigatran use is superior to that of warfarin because, with comparable effectiveness, dabigatran was associated with lower rates of recurrent bleeding. In contrast, we observed that the use of dabigatran was substantially less common than the use of warfarin among patients who survived a major bleeding event in 2010 to 2012. The lower tendency to prescribe dabigatran as compared with warfarin after a major hemorrhage in 2010 to 2012 may be explained by 2 reasons. First, although warfarin therapy requires routine international normalized ratio monitoring, laboratory coagulation markers are not routinely monitored for patients on dabigatran. In this context, clinicians may be under the impression that they have more control over the coagulation status of patients on warfarin than those on dabigatran, particularly in the early aftermath of a major bleeding event. Second, clinicians may have been especially risk-averse to prescribe dabigatran during our study period because of the warnings on the risk of severe bleeding with dabigatran released by the main international regulatory agencies throughout 2011, as well as the lack of antidote to reverse the anticoagulation effects of dabigatran in the time period that this study captures. In this scenario, patients who were prescribed dabigatran after the index hemorrhage were likely to be those at lowest risk of recurrent bleeding. These risk-averse prescription patterns of dabigatran may have introduced residual confounding in our results for the comparative risk of bleeding events with warfarin and dabigatran. With the approval in October 2015 of idarucizumab, a dabigatran-binding monoclonal antibody fragment, prescribers may become more comfortable using dabigatran in patients who have already suffered a major bleeding event on anticoagulation. Therefore, it will be important to repeat analyses similar to ours because newer Medicare Part D data that represents the period after the approval of idarucizumab become available.

Study Limitations

In addition to the fact that our results reflect the early experience with dabigatran, our study is subject to 3 main limitations. First, claims data do not contain laboratory results and, therefore, we did not have information about the international normalized ratio levels of our study subjects, which may

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**Figure 4.** Adjusted hazard ratios of posthemorrhage clinical outcomes. Bold denotes statistical significant results. Hazard ratios were estimated with Cox proportional hazard models. CI indicates confidence interval.
have affected the decision to restart anticoagulation therapy in patients who bled on warfarin. Second, we did not stratify our analyses by the anatomic location of the index bleeding event. The posthemorrhage clinical outcomes of patients experiencing an intracranial bleeding, for example, are likely to be different from those who presented with a gastrointestinal bleeding. Third, we did not stratify by the dose of dabigatran used. Nevertheless, the use of dabigatran 75 mg was relatively uncommon in the period that our study represents—<10% of Medicare beneficiaries with AF on dabigatran were prescribed dabigatran 75 mg in the first 2 years after dabigatran approval.14

Conclusions
In this observational study, the resumption of anticoagulation with either dabigatran or warfarin after a major bleeding event was associated with increased survival and stroke-free survival compared with discontinuing anticoagulation. In addition, dabigatran was associated with lower risk of recurrent hemorrhage than warfarin. Our findings suggest that the benefit/risk ratio of dabigatran in the prevention of stroke among AF patients who have survived a major hemorrhage is superior to that of warfarin therapy or anticoagulation discontinuation but will need to be validated in other patient cohorts and with more recent data.

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References


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SUPPLEMENTAL MATERIAL

Supplemental Methods

Frequency Matching

To select a day to start following patients who interrupted anticoagulation after the index major hemorrhage, we performed frequency matching. To do so, we simulated the distribution of the time to restart of anticoagulation for the groups that filled a prescription for an oral anticoagulation agent after the index major hemorrhage. The time to restart of drug in the dabigatran cohort followed a gamma distribution with $\alpha=1.17$ and $\sigma=47.5$. The time to restart of drug in the warfarin cohort followed a gamma distribution with $\alpha=1.12$ and $\sigma=54.2$. Start date after index major hemorrhage was set up so that the window between the date of the index major hemorrhage and start date followed a similar distribution to that of the time to anticoagulation restart among the subjects that restarted anticoagulation after the index major bleeding event.

Definition of Outcomes

A major bleeding event included any inpatient claims with primary or secondary ICD-9 codes for intracranial hemorrhage, hemoperitoneum, genitourinary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemothysis, vaginal hemorrhage, hemarthrosis, conjunctival hemorrhage or not otherwise specified hemorrhage (the list of ICD-9 codes is displayed in Table I). Any bleeding event included any inpatient, emergency room or outpatient claim with primary or secondary ICD-9 codes for the same list of bleeding events. In order to avoid double counting, several claims for a bleeding event were considered the same single event if they occurred within 2 weeks of each other.

Definition of Covariates

CHA2DS2-Vasc score measures of the risk of stroke in patients with AF. To calculate CHA2DS2-Vasc, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points.

HAS-BLED score is a prediction score of the risk of major bleeding for patients with AF on anticoagulation. In calculating the HAS-BLED, age of 65 or greater, labile INR, renal disease, liver disease, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs (NSAIDs), and a history of hypertension, of stroke, of major bleeding and of alcohol or drug use are all assigned one point. Because claims data does not contain information on INR, we calculated the HAS-BLED score as the sum of all previous factors except labile INR.

The number of other CMS priority comorbidities was calculated as the sum of previous a history of acquired hypothyroidism, Alzheimer’s disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer and endometrial cancer.

Vascular disease was defined as having at least one outpatient claim with primary or secondary ICD-9 codes 440.0x, 440.2x, 440.9x, 441.3x, 441.4x, 441.5x, 441.9x, 443.9x, 444.22, 444.81, 447.1x, 447.81, 250.70, 433.10, 433.11, 433.30 in the year before index major hemorrhage.

Liver disease was defined as having at least one outpatient claim with primary or secondary ICD-9 code 571.xx in the year before index major hemorrhage.

Alcohol or drug usage history was defined as having at least one outpatient claim with primary or secondary ICD-9 codes 303.xx, 304.xx, 305.xx in the year before index major hemorrhage.
Use of NSAIDS was defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin in the six months before the date of the first major hemorrhage; and use of antiplatelet drugs was defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine or ticagrelor in the six months before the date of the index major hemorrhage.¹

Receiving a transfusion was defined as having at least one procedure with ICD-9 procedure code 990.xx during the inpatient stay for the index bleeding event.

To identify which patients underwent a corrective surgical procedure, we extracted all ICD-9 procedure codes recorded during the inpatient stay for the index major hemorrhage, and selected the procedures whose objective was to correct the anatomical area where the bleeding event had happened (the list of qualifying ICD-9 procedure codes for corrective surgical procedures in each anatomical area can be found in Table I at http://stroke.ahajournals.org).

To identify a history of chronic kidney disease, hypertension, stroke or transient ischemic attack, acute myocardial infarction, diabetes, and congestive heart failure, we used the CMS Chronic Condition Warehouse (CCW) indicators that trace back the diagnosis of these conditions to January 1, 1999.⁷
Supplemental Table I. International Classification of Diseases, Ninth Revision (ICD-9) Codes for Bleeding Events and for Corrective Surgical Procedures by Anatomical Site.

<table>
<thead>
<tr>
<th>Bleeding Event</th>
<th>ICD-9 Diagnosis Codes to Identify Bleeding Events</th>
<th>ICD-9 Procedure Codes to Identify Corrective Procedures</th>
</tr>
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<tbody>
<tr>
<td>Intracranial bleeding</td>
<td>430, 431, 432</td>
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<tr>
<td>Hemoperitoneum</td>
<td>568.81</td>
<td>54.12, 54.4</td>
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<tr>
<td>Hematuria</td>
<td>599.7, 530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 536.9, 536.21, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.85, 578</td>
<td>42.33, 43.41, 43.89, 44.29, 44.42, 44.43, 44.44, 45.30, 45.34, 45.42, 45.43, 45.73, 45.74, 45.76, 45.82, 45.93, 46.20, 48.35, 48.36</td>
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<tr>
<td>GI Hemorrhage</td>
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<td></td>
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<tr>
<td>Epistaxis</td>
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<td>21.01, 21.02, 21.03, 21.05, 21.31, 21.61</td>
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<tr>
<td>Epistaxis</td>
<td>786.3</td>
<td>30.29, 31.1, 31.69, 32.20</td>
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<td>Vaginal Hemorrhage</td>
<td>623.8, 626.2</td>
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<td>Hemarthrosis</td>
<td>719.1, 719.2</td>
<td>81.92</td>
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<tr>
<td>Conjunctival hemorrhage</td>
<td>372.72</td>
<td>12.4</td>
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<tr>
<td>NOS Hemorrhage</td>
<td>459</td>
<td>Any of the listed codes</td>
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Notes:

Abbreviations: GI=Gastrointestinal; NOS=Not Otherwise Specified.
**Supplemental Table II. Time to Post-Hemorrhage Anticoagulation Resumption, Follow-up Period, and Patterns of Post-Hemorrhage Anticoagulation Use, by Treatment Group and Study Cohort.**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Cohort- Mean (SD)</th>
<th>Warfarin Cohort- Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resumed Dabigatran (n=117)</td>
<td>No Oral Anticoagulant Use (n=626)</td>
</tr>
<tr>
<td>Time from first major bleeding to anticoagulant re-start (days)</td>
<td>45 (49)</td>
<td>--</td>
</tr>
<tr>
<td>Follow-up period after first major bleeding (days)</td>
<td>396 (167)</td>
<td>335 (201)</td>
</tr>
<tr>
<td>Patterns of post-hemorrhage anticoagulant use (%)</td>
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<td></td>
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<tr>
<td>Switched anticoagulant treatment</td>
<td>18.0</td>
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</tr>
<tr>
<td>Discontinued anticoagulant therapy</td>
<td>3.4</td>
<td>--</td>
</tr>
<tr>
<td>Time from first major bleeding to anticoagulant re-start (days)</td>
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<td></td>
</tr>
<tr>
<td>Full cohort</td>
<td>60 (72)</td>
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</tr>
<tr>
<td>Patients with intracranial index bleeding</td>
<td>109 (77)</td>
<td>64 (64)</td>
</tr>
<tr>
<td>Follow-up period after first major bleeding (days)</td>
<td>371 (205)</td>
<td>333 (205)</td>
</tr>
<tr>
<td>Patterns of post-hemorrhage anticoagulant use (%)</td>
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<td></td>
</tr>
<tr>
<td>Switched anticoagulant treatment</td>
<td>3.1</td>
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</tr>
<tr>
<td>Discontinued anticoagulant therapy</td>
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<td>Dabigatran Cohort</td>
<td>Resumed Dabigatran (n=117)</td>
<td>No Oral Anticoagulation (n=217)</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------</td>
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</tr>
<tr>
<td><strong>Effectiveness Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic Stroke and All-Cause Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>21 (18.0)</td>
<td>48 (22.1)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>0.07 (0.02, 0.12)</td>
<td>0.18 (0.13, 0.24)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>0.13 (0.07, 0.19)</td>
<td>0.21 (0.15, 0.27)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.21 (0.13, 0.29)</td>
<td>0.26 (0.19, 0.33)</td>
</tr>
<tr>
<td>At 1 yr</td>
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<td></td>
</tr>
<tr>
<td><strong>Ischemic Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>20 (17.1)</td>
<td>23 (10.6)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>0.06 (0.02, 0.11)</td>
<td>0.07 (0.03, 0.11)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>0.12 (0.06, 0.18)</td>
<td>0.08 (0.04, 0.13)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.20 (0.12, 0.29)</td>
<td>0.15 (0.08, 0.21)</td>
</tr>
<tr>
<td>At 1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>2 (1.7)</td>
<td>25 (11.5)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>0.01 (0.00, 0.03)</td>
<td>0.12 (0.07, 0.16)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>0.02 (0.00, 0.04)</td>
<td>0.13 (0.08, 0.18)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.02 (0.00, 0.04)</td>
<td>0.13 (0.08, 0.18)</td>
</tr>
<tr>
<td>At 1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Major Recurrent Hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>8 (6.8)</td>
<td>13 (6.0)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>0.04 (0.00, 0.07)</td>
<td>0.05 (0.02, 0.08)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>0.06 (0.01, 0.10)</td>
<td>0.05 (0.02, 0.09)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.07 (0.02, 0.11)</td>
<td>0.09 (0.04, 0.14)</td>
</tr>
<tr>
<td>At 1 yr</td>
<td></td>
<td></td>
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<tr>
<td><strong>Any Recurrent Hemorrhage</strong></td>
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<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>40 (34.2)</td>
<td>60 (27.7)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>0.24 (0.16, 0.32)</td>
<td>0.24 (0.18, 0.30)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>0.29 (0.21, 0.37)</td>
<td>0.31 (0.24, 0.38)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.34 (0.25, 0.44)</td>
<td>0.40 (0.31, 0.49)</td>
</tr>
<tr>
<td>At 1 yr</td>
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<tr>
<td>Warfarin Cohort</td>
<td>Resumed Warfarin (n=484)</td>
<td>No Oral Anticoagulation (n=626)</td>
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<tr>
<td>----------------</td>
<td>--------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Effectiveness Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke and All-Cause Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>92 (19.0)</td>
<td>144 (23.0)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>At 3 months: 0.10 (0.07, 0.13)</td>
<td>0.20 (0.17, 0.23)</td>
</tr>
<tr>
<td>At 6 months: 0.16 (0.12, 0.19)</td>
<td>0.23 (0.20, 0.27)</td>
<td>0.23 (0.05, 0.40)</td>
</tr>
<tr>
<td>At 1 yr: 0.23 (0.18, 0.27)</td>
<td>0.26 (0.23, 0.30)</td>
<td>0.28 (0.09, 0.48)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>Number of events (%)</td>
<td>66 (13.6)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>At 3 months: 0.06 (0.04, 0.09)</td>
<td>0.09 (0.06, 0.11)</td>
</tr>
<tr>
<td>At 6 months: 0.11 (0.07, 0.14)</td>
<td>0.11 (0.08, 0.14)</td>
<td>0.19 (0.02, 0.36)</td>
</tr>
<tr>
<td>At 1 yr: 0.17 (0.13, 0.21)</td>
<td>0.14 (0.11, 0.18)</td>
<td>0.25 (0.06, 0.44)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>Number of events (%)</td>
<td>27 (5.6)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>At 3 months: 0.03 (0.02, 0.05)</td>
<td>0.14 (0.11, 0.17)</td>
</tr>
<tr>
<td>At 6 months: 0.06 (0.03, 0.08)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.04 (0.00, 0.13)</td>
</tr>
<tr>
<td>At 1 yr: 0.07 (0.04, 0.09)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.04 (0.00, 0.13)</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td>Major Recurrent Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>68 (14.1)</td>
<td>44 (7.0)</td>
</tr>
<tr>
<td>Cumulative incidence (95% CI)</td>
<td>At 3 months: 0.08 (0.06, 0.11)</td>
<td>0.06 (0.04, 0.08)</td>
</tr>
<tr>
<td>At 6 months: 0.11 (0.08, 0.14)</td>
<td>0.08 (0.06, 0.11)</td>
<td>0.00 (0.00, 0.00)</td>
</tr>
<tr>
<td>At 1 yr: 0.17 (0.13, 0.21)</td>
<td>0.10 (0.07, 0.13)</td>
<td>0.00 (0.00, 0.00)</td>
</tr>
<tr>
<td>Any Recurrent Hemorrhage</td>
<td>Number of events (%)</td>
<td>170 (35.1)</td>
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<tr>
<td>Cumulative incidence (95% CI)</td>
<td>At 3 months: 0.26 (0.22, 0.30)</td>
<td>0.29 (0.25, 0.33)</td>
</tr>
<tr>
<td>At 6 months: 0.33 (0.29, 0.38)</td>
<td>0.35 (0.30, 0.39)</td>
<td>0.17 (0.02, 0.33)</td>
</tr>
<tr>
<td>At 1 yr: 0.42 (0.37, 0.47)</td>
<td>0.39 (0.34, 0.43)</td>
<td>0.17 (0.02, 0.33)</td>
</tr>
</tbody>
</table>

**NOTES:**
Cumulative incidence of clinical events was calculated from Kaplan-Meier time-to-event curves.
### Supplemental Table IV. Anatomical Location of the Recurrent Bleeding Event, by Anatomical Location of the First Major Hemorrhage and Treatment Group.

<table>
<thead>
<tr>
<th>Location of Any Recurrent Bleeding Event</th>
<th>Dabigatran Cohort</th>
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<th></th>
<th></th>
<th></th>
<th>Warfarin Cohort</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Resumed Dabigatran</td>
<td>Resumed Warfarin</td>
<td>Other</td>
<td>No Bleeding</td>
<td>Resumed Dabigatran</td>
<td>Resumed Warfarin</td>
<td>Other</td>
<td>No Bleeding</td>
<td>Resumed Dabigatran</td>
<td>Resumed Warfarin</td>
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<tr>
<td>IC (n=0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (25.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>GI (n=92)</td>
<td>1 (1.1)</td>
<td>22 (23.9)</td>
<td>3 (3.3)</td>
<td>3 (3.3)</td>
<td>63 (68.5)</td>
<td>5 (1.2)</td>
<td>85 (25.2)</td>
<td>5 (1.5)</td>
<td>21 (6.2)</td>
<td>222 (65.9)</td>
</tr>
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<td>Hematuria (n=5)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>2 (40.0)</td>
<td>0 (0.0)</td>
<td>2 (40.0)</td>
<td>1 (2.4)</td>
<td>0 (0.0)</td>
<td>11 (26.2)</td>
<td>4 (9.5)</td>
<td>26 (61.9)</td>
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<tr>
<td>Other (n=20)</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>5 (25.0)</td>
<td>12 (60.0)</td>
<td>2 (2.4)</td>
<td>10 (11.8)</td>
<td>3 (3.5)</td>
<td>17 (20.0)</td>
<td>53 (62.4)</td>
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<tr>
<td>Switched to Warfarin</td>
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<tr>
<td>IC (n=5)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
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<tr>
<td>GI (n=53)</td>
<td>1 (1.1)</td>
<td>16 (30.2)</td>
<td>2 (3.8)</td>
<td>3 (5.7)</td>
<td>31 (58.5)</td>
<td>0 (0.0)</td>
<td>3 (15.8)</td>
<td>1 (5.3)</td>
<td>1 (53.3)</td>
<td>14 (74.7)</td>
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<td>Hematuria (n=2)</td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<td>0 (0.0)</td>
<td>1 (10.0)</td>
<td>8 (80.0)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
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<tr>
<td>No Post-Hemorrhage Oral Anticoagulation Use</td>
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<tr>
<td>IC (n=23)</td>
<td>5 (21.7)</td>
<td>1 (4.35)</td>
<td>1 (4.35)</td>
<td>1 (4.35)</td>
<td>15 (65.2)</td>
<td>26 (22.4)</td>
<td>2 (1.7)</td>
<td>3 (2.6)</td>
<td>3 (2.6)</td>
<td>82 (70.7)</td>
</tr>
<tr>
<td>GI (n=184)</td>
<td>1 (0.5)</td>
<td>38 (20.7)</td>
<td>5 (2.7)</td>
<td>6 (3.3)</td>
<td>134 (72.8)</td>
<td>3 (0.7)</td>
<td>107 (25.1)</td>
<td>8 (1.9)</td>
<td>12 (2.8)</td>
<td>296 (69.5)</td>
</tr>
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<td>1 (20.0)</td>
<td>0 (0.0)</td>
<td>4 (80.0)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>4 (22.2)</td>
<td>0 (0.0)</td>
<td>13 (72.2)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
<td>0 (0.0)</td>
<td>4 (6.1)</td>
<td>2 (3.0)</td>
<td>13 (19.7)</td>
<td>47 (71.2)</td>
</tr>
</tbody>
</table>

**NOTES:**

Abbreviations: IC=Intracranial; GI=Gastrointestinal.
**Supplemental Table V. Results of Sensitivity Analyses.**

<table>
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<th></th>
<th>Resumed Dabigatran vs No Oral Anticoagulant Use</th>
<th>Switched to Warfarin vs No Oral Anticoagulant Use</th>
<th>Switched to Warfarin vs Resumed Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Hazard Ratio (% CI)</td>
<td>Adjusted Hazard Ratio (% CI)</td>
<td>Adjusted Hazard Ratio (% CI)</td>
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<td><strong>Effectiveness Outcomes</strong></td>
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<tr>
<td>Ischemic Stroke/All-Cause Mortality</td>
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<td></td>
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</tr>
<tr>
<td>Resumed Dabigatran cohort</td>
<td>Sensitivity Analysis</td>
<td>0.64 (0.38-1.10)</td>
<td>0.57 (0.28-1.14)</td>
</tr>
<tr>
<td>Switched to Warfarin vs No Oral Anticoagulant Use</td>
<td>Base Case</td>
<td>0.67 (0.40-1.15)</td>
<td>0.70 (0.38-1.31)</td>
</tr>
<tr>
<td>Switched to Dabigatran vs No Oral Anticoagulant Use</td>
<td>Sensitivity Analysis</td>
<td>0.11 (0.01-0.82)</td>
<td>0.21 (0.05-0.91)</td>
</tr>
<tr>
<td>Switched to Dabigatran vs Resumed Warfarin</td>
<td>Base Case</td>
<td>0.13 (0.03-0.56)</td>
<td>0.13 (0.03-0.58)</td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Recurrent Hemorrhage</td>
<td>0.71 (0.28-1.83)</td>
<td>0.68 (0.27-1.72)</td>
<td>1.20 (0.44-3.30)</td>
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<tr>
<td>Any Recurrent Hemorrhage</td>
<td>0.91 (0.60-1.39)</td>
<td>0.87 (0.58-1.32)</td>
<td>1.23 (0.76-1.98)</td>
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<tr>
<td><strong>Warfarin cohort</strong></td>
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</tr>
<tr>
<td>Ischemic Stroke/All-Cause Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resumed Warfarin vs No Oral Anticoagulant Use</td>
<td>Sensitivity Analysis</td>
<td>0.71 (0.54-0.95)</td>
<td>0.75 (0.57-0.98)</td>
</tr>
<tr>
<td>Switched to Dabigatran vs No Oral Anticoagulant Use</td>
<td>Base Case</td>
<td>0.75 (0.57-0.98)</td>
<td>0.96 (0.42-2.19)</td>
</tr>
<tr>
<td>Switched to Dabigatran vs Resumed Warfarin</td>
<td>Sensitivity Analysis</td>
<td>0.35 (0.22-0.55)</td>
<td>0.35 (0.23-0.55)</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Recurrent Hemorrhage</td>
<td>1.63 (1.09-2.44)</td>
<td>1.60 (1.09-2.36)</td>
<td>0.42 (0.06-3.06)</td>
</tr>
<tr>
<td>Any Recurrent Hemorrhage</td>
<td>0.94 (0.75-1.18)</td>
<td>0.95 (0.77-1.18)</td>
<td>0.50 (0.20-1.21)</td>
</tr>
</tbody>
</table>
### Supplemental Table V continued

<table>
<thead>
<tr>
<th>Two cohorts combined</th>
<th>Warfarin vs No Oral Anticoagulant Use</th>
<th>Dabigatran vs No Oral Anticoagulant Use</th>
<th>Dabigatran vs Warfarin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity Analysis</td>
<td>Base Case</td>
<td>Sensitivity Analysis</td>
</tr>
<tr>
<td><strong>Effectiveness Outcomes</strong></td>
<td></td>
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</tr>
<tr>
<td>Ischemic Stroke/All-Cause Mortality</td>
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<tr>
<td>All-Cause Mortality</td>
<td>0.71 (0.55-0.92)</td>
<td>0.76 (0.59-0.97)</td>
<td>0.60 (0.39-0.93)</td>
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<tr>
<td>Ischemic Stroke</td>
<td>0.33 (0.22-0.51)</td>
<td>0.35 (0.23-0.53)</td>
<td>0.13 (0.04-0.41)</td>
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<tr>
<td><strong>Safety Outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Major Recurrent Hemorrhage</td>
<td>1.24 (0.76-2.02)</td>
<td>1.27 (0.93-1.75)</td>
<td>1.24 (0.88-1.76)</td>
</tr>
<tr>
<td>Any Recurrent Hemorrhage</td>
<td>0.99 (0.81-1.21)</td>
<td>0.97 (0.80-1.17)</td>
<td>0.80 (0.58-1.11)</td>
</tr>
</tbody>
</table>

**Notes:**

Bold denotes statistical significant results.

Results from sensitivity analyses represent adjusted hazard ratios of post-hemorrhage clinical outcomes calculated before and after excluding patients who experienced an intracranial bleeding event.
Supplemental References