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Dabigatran versus Rivaroxaban for Secondary Stroke Prevention in Patients with Atrial Fibrillation Rehabilitated in Skilled Nursing Facilities

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Abstract

Background: Thromboembolic and bleeding risk are elevated in older patients with atrial fibrillation and prior stroke. We compared dabigatran versus rivaroxaban for secondary prevention in a national population after skilled nursing facility (SNF) discharge.

Methods: Medicare fee-for-service beneficiaries aged ≥ 65 years with atrial fibrillation hospitalized for ischemic stroke (11/2011–10/2013) and subsequently admitted to a SNF were studied. Dabigatran (n=332) and rivaroxaban users (n=378) were compared in a retrospective, active comparator, new-user cohort. The index medication claim occurred within 120 days after hospital discharge and exposure continued until a 14-day treatment gap (“as treated”). The primary net clinical benefit outcome was the time to recurrent stroke, transient ischemic attack, intracranial hemorrhage, extracranial bleed, myocardial infarction, venous thromboembolism, or death. All-cause mortality was evaluated separately as a secondary outcome. Multivariable adjusted Cox models stratified by dosage estimated hazard ratios (aHR).

Results: Among those receiving low dosages, the crude composite event rate was 40.4/100 person-years among dabigatran users and 33.7/100 person-years among rivaroxaban users. The

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Compliance with Ethical Standards: The University of Massachusetts Medical School Institutional Review Board approved this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of research formal consent is not required.

composite outcome (aHR: 1.48; 95% Confidence Interval (CI): 0.87–2.51) and all-cause mortality (aHR: 1.67; 95%CI: 0.84–3.31) rates were higher among low dose dabigatran users. For those receiving standard doses, the crude composite event rates were 19.5/100 person-years for dabigatran users and 37.1/100 person-years for rivaroxaban users. Although no difference in mortality was observed, the composite outcome rate was lower among standard dose dabigatran users (aHR: 0.65; 95%CI: 0.36–1.15).

Conclusions: In older adults treated with direct-acting oral anticoagulants after ischemic stroke, outcome rates varied considerably by drug and dosage.

1. Introduction

Decisions regarding the use of anticoagulation for older adults with atrial fibrillation are complicated by polypharmacy and multiple comorbidities [1, 2], along with greater risk of post-stroke disability and mortality [3]. After an ischemic stroke, nearly one-third of Medicare enrollees are discharged to skilled nursing facilities (SNFs) [4]. Post-stroke Medicare patients entering SNFs are older than patients returning home and have a high prevalence of sociodemographic and clinical risk factors for stroke and bleeding events [4].

Anticoagulant switching and initiation is common following ischemic stroke [5]. Comparative effectiveness research and evidence specific to post-stroke patients receiving care in SNFs remains limited for the newer and increasingly utilized direct-acting oral anticoagulants (DOACs). When used for secondary stroke prevention at standard doses, dabigatran and rivaroxaban have been reported to have similar risk for thromboembolic events, bleeding events, and all-cause mortality based upon indirect treatment comparisons using trial data [6–7]. Recent observational studies focused on patients treated for primary prevention have, however, suggested an increased risk of bleeding and mortality with rivaroxaban at both the renal (75mg dabigatran, 15mg rivaroxaban) and standard doses (150mg dabigatran, 20mg rivaroxaban) [8–9]. Single-center studies of DOACs post-stroke have described variability in recurrence risk and recurrent stroke volume for rivaroxaban, dabigatran, and apixaban [10–11].

The objective of this observational study was to estimate the net clinical benefit of treatment with dabigatran versus rivaroxaban for secondary stroke prevention after discharge from a SNF after an ischemic stroke.

2. Methods

2.1 Data

Medicare administrative files and the Minimum Data Set (MDS) 3.0 were used for the present study through a data use agreement with the Centers for Medicare and Medicaid Services. Vital and eligibility information from the Medicare Master Beneficiary Summary File, inpatient and SNF records from Medicare Part A, prescription dispensing records from the Medicare Part D Event and Characteristics Files, and SNF/long-stay nursing home MDS 3.0 assessment records were linked. All Medicare and Medicaid certified nursing facilities are required to complete MDS 3.0 assessments for residents at admission and specified intervals. The validity of the MDS 3.0 data has been previously described [12].

2.2 Study Design

An active comparator new-user design among patients with atrial fibrillation admitted to a SNF after an ischemic stroke compared initiators of dabigatran or rivaroxaban, reducing the potential for confounding by indication and selection bias [13]. A comparison to apixaban was not made due to low utilization (approved 12/2012) during our study period. Because Medicare Part D does not reimburse for medications in SNFs, the first observed claim (i.e., outside of the SNF) served as the index date. Patients were followed from the initiation of dabigatran or rivaroxaban (index date) until the first occurrence of either a study event, discontinuation of the index medication (a gap in days covered of >14 days), switch to another oral anticoagulant, change in dose of the index anticoagulant, end of enrollment in Medicare fee-for-service Parts A, B, and D, or end of data availability (12/31/2013).

2.3 Sample Selection

Medicare fee-for-service beneficiaries diagnosed with atrial fibrillation who were aged 65 years, hospitalized for an ischemic stroke from November 04, 2011 (the marketing approval date for rivaroxaban) to October 02, 2013, discharged to a SNF post-stroke, and who newly initiated rivaroxaban or dabigatran post-stroke were included (Electronic Supplementary Material). Ischemic stroke hospitalizations were identified using International Classification of Diseases 9th Edition (ICD-9) diagnosis codes in the primary position [14] and patients with atrial fibrillation/flutter were identified using codes in any non-primary position on the index hospitalization claim (Electronic Supplementary Material). We only included patients admitted to a Medicare certified SNF within 30 days after hospital discharge to obtain a relatively homogeneous population who experienced a moderate-to-severe stroke requiring rehabilitation.

The first Part D claim for dabigatran or rivaroxaban within 120-days after hospital discharge served as the index date, avoiding immortal time bias. The 120-day indexing period allowed 20 days beyond the maximum Medicare reimbursed SNF length of stay (100 days) to ascertain the dispensing of outpatient medications. The study population included a mix of patients who initiated dabigatran or rivaroxaban in the hospital/SNF, those who newly initiated after SNF discharge, and those who used another anticoagulant during the SNF stay and subsequently switched to dabigatran or rivaroxaban after discharge.

Patients without a 90-day baseline period prior to the stroke hospitalization with continuous enrollment in Medicare fee-for-service were excluded. Patients with a hospitalization or SNF discharge in the 30 days preceding the stroke hospitalization were excluded to obtain a more clinically stable sample. Patients readmitted to the hospital before admission to a SNF, comatose patients, and hospice patients were also excluded.

2.4 Dabigatran or Rivaroxaban Use

To implement the “as-treated” approach, we estimated daily use of dabigatran or rivaroxaban using fill dates and number of days supplied from Part D claims. Each post-index day was marked as covered if the supply from the most recent dispensing was sufficient to cover that day, accounting for medication accumulation and inpatient stays. Days without coverage by

the index medication represented a gap in treatment and the patient was censored upon the first day exceeding a 14-day gap (i.e., the 15th consecutive day without medication).

Due to differences in patient characteristics by anticoagulant dose, the index dose (i.e., the dosage on the index claim) was recorded for each medication as either standard (dabigatran 150mg or rivaroxaban 20mg) or less than standard (dabigatran 75mg or rivaroxaban 10mg or 15mg). Although rivaroxaban 10mg is not indicated for the prevention of stroke in patients with nonvalvular atrial fibrillation, we included patients using this off-label dosage because DOAC underdosing is common among older adults and few studies have examined this dose [15–16]. No rivaroxaban 10mg initiators had a diagnosis of venous thromboembolism (VTE) at the time of their index hospitalization.

2.5 Outcomes

The primary time-to-event net clinical benefit outcome was defined as the number of days from the index date to a hospital admission for ischemic stroke, transient ischemic attack, VTE, myocardial infarction, intracranial hemorrhage, extracranial bleeding, or death. This composite outcome was chosen to inform the real-world choice facing patients and clinicians, which requires simultaneous consideration of several major safety and effectiveness outcomes. The composite outcome approximated the net clinical benefit outcome from the Phase 3 RE-LY trial of dabigatran versus warfarin [17]. Each component clinical event was identified using validated ICD-9 based algorithms from subsequent hospitalizations (Supplementary Material) [14, 18–20], underscoring the acuity of each condition and supporting aggregation into a single outcome. All-cause mortality was separately evaluated as a secondary outcome, defined as the number of days from index until a verified Medicare death date.

2.6 Covariates

Covariates included demographics, select comorbid conditions known to increase the risk of ischemic or bleeding events (CHADS₂ (used due to lack of historical information on the vascular component of CHA₂DS₂-VASc) and available components of HAS-BLED risk score) [21–22], cancer, active pressure ulcer, length of index hospital stay, long-term nursing home residence, pre-stroke SNF stay, pre-stroke hospitalization, bleeding (intracranial or extracranial) during the index stroke hospitalization, medication regimen complexity, medication use, post-stroke pre-index inpatient rehabilitation, cognitive status, and functioning in activities of daily living (ADLs). Recent history of bleeding complications (extracranial and cerebral bleeding codes, any diagnostic position) [18] and acute treatment (tissue plasminogen activator, mechanical thrombectomy) were defined using ICD-9 codes from the index stroke hospitalization. With the exception of chronic renal insufficiency (CRI), which was identified from the index hospital claim [23], comorbid disease information, cognitive impairment, and ADLs were defined using the first SNF MDS 3.0 assessment.

Cognitive impairment was captured using the 4-category MDS 3.0 Cognitive Function Scale [24]. Data on ADLs from the MDS 3.0 [25] were used to score each patient's post-stroke function with Shah's modified Barthel Index (Electronic Supplementary Material), which

maintains the point distribution from the original scale but improves sensitivity by awarding points for performance with varying levels of assistance [26]. Medication regimen complexity was the number of claims for unique medication-dose combinations during the 90-day baseline. Individual medications were identified during the 90-days before the index stroke and the days after stroke hospitalization but before the index dispensing. Information was collected on the use of antiplatelets, non-steroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors since these medications are bleeding risk factors, and on beta blockers, ACE-inhibitors/ARBs, statins, and diuretics because these medications are recommended for secondary stroke and myocardial infarction prevention.

2.7 Statistical Analysis

Descriptive statistics for baseline characteristics by treatment and dosage group included frequencies and percentages for categorical variables and medians with first and third quartiles for continuous variables. Kaplan Meier curves with accompanying log rank tests were constructed for the composite outcome and the all-cause mortality outcome. Cox proportional hazards models stratified according to dose compared the outcome rate between dabigatran users and rivaroxaban users adjusted for the pre-specified variables age, sex, antiplatelet use, bleeding history, post-stroke inpatient rehabilitation, Barthel Index, cognitive impairment, and CHADS₂ score. No other covariates changed the measure of association by 10%. The proportional hazards assumption was tested and satisfied for each model. We also performed an analysis within the low dose cohort without the 10mg off-label rivaroxaban dose.

3. Results

3.1 Baseline Characteristics

In the post-stroke period, 332 and 378 patients initiated dabigatran and rivaroxaban, respectively. The median age of the cohort was 84 years (Q1: 79, Q3: 88), 72.0% of patients were women, and 86.1% were non-Hispanic white. Functional impairment was common at SNF admission (median Barthel Index: 40; Q1: 29, Q3: 54), as were stroke risk factors (29% of patients diagnosed with diabetes, 22% with heart failure, 87% with hypertension, 83% 75 years of age), resulting in a cohort where 87% had a CHADS₂ score 4 (Table 1). Most patients (88%) resided in the community pre-stroke.

3.2 Follow-up

The median duration of on-treatment follow-up was 116 days (Q1: 44, Q3: 244), with 177 and 162 person-years contributed by dabigatran and rivaroxaban exposed patients, respectively. Nearly all (98%) prescriptions for dabigatran and rivaroxaban were for the labeled dosing frequency (once and twice daily, respectively). The proportion of days covered was 80% for 87.1% of dabigatran and 90.5% of rivaroxaban users. During the follow-up period, 114 events occurred among 108 (15.2%) patients, including 57 deaths. No patient experienced two clinical events, however six experienced a clinical event and subsequently died while exposed. Among patients who experienced a composite event, the median time to event was 44 days (Q1: 17, Q3: 127) for 51 dabigatran treated patients and 44 days (Q1: 18, Q3: 116) for 57 rivaroxaban treated patients.

3.3 Low Dose

In the low dose cohort, crude incidence rates for the composite outcome were 40.4 per 100 person-years among dabigatran users and 33.7 events per 100 person-years among rivaroxaban users (Table 2). The crude incidence of ischemic stroke and bleeding (intracranial and extracranial) among dabigatran users was 1.4 and 11.5 events per 100-person years, respectively, while the crude incidence of ischemic stroke and bleeding among rivaroxaban users was 10.1 and 3.4 events per 100 person-years, respectively. Among patients with CRI using low doses of either anticoagulant, no ischemic stroke events occurred. Bleeding incidence among low dose dabigatran users with CRI was 16.3 events per 100-person-years, while no bleeding events occurred among low dose rivaroxaban users with CRI.

The Kaplan Meier curve for the composite outcome depicts a decline in the survival probability for each treatment group (Log-rank p-value=0.23) until flattening at ~0.8 after 6 months of follow-up (Figure 1). The unadjusted hazard ratio for the composite outcome (dabigatran versus rivaroxaban) was 1.37 (95% CI: 0.81–2.30) with a similar estimate derived from the adjusted model (Table 3). When the 50 rivaroxaban 10mg users were excluded, the adjusted hazard ratio for the composite outcome (dabigatran 75mg versus rivaroxaban 15mg) was 1.55 (95% CI: 0.88–2.75).

3.4 Standard Dose

Crude incidence rates for the composite outcome were 19.5 per 100 person-years among dabigatran 150mg users and 37.1 per 100 person-years among rivaroxaban 20mg users. Kaplan Meier curves (Figure 1) flattened at 6 months for dabigatran users and 9 months for rivaroxaban users (log rank p-value=0.13). In unadjusted models, the hazard ratio for the composite outcome (dabigatran versus rivaroxaban) was 0.65 (95% CI: 0.37–1.15), with a similar estimate in the adjusted model.

3.5 Secondary Outcome of All-Cause Mortality

Little difference was observed in the Kaplan Meier curves for all-cause mortality in both dosage cohorts (Figure 2). For the less than standard dose cohort, the adjusted hazard ratio comparing dabigatran to rivaroxaban users was 1.67 (95% CI: 0.84–3.31). Among standard dose patients, no strong association between treatment and all-cause mortality was observed (aHR: 1.05; 95% CI: 0.45–2.47).

4. Discussion

Patients requiring rehabilitation in a SNF after an ischemic stroke are a medically complex older population with high prevalence of stroke risk factors, many of whom suffer from severe cognitive impairment and functional limitations. High rates of ischemic events, bleeding, and all-cause mortality were observed in our study population. Although we found no clear of advantage of one medication over the other, our findings suggest that labeled dosing recommendations have consequences for patient outcomes that may differ by DOAC. With little to no clinical trial data on rivaroxaban 10mg and 15 mg and dabigatran 15mg

(particularly in high-risk post-stroke populations), clinicians and patients should consider observational evidence and be wary of deviating from labeled dosing recommendations.

During the ~2 years following rivaroxaban's approval, 21% of SNF rehabilitated patients initiating oral anticoagulants post-stroke were treated with dabigatran or rivaroxaban. Users of DOACs were adherent, in agreement with the literature [27]. The pace of diffusion of DOACs in this older patient population is consistent with previous research. In the two years following dabigatran's approval, DOAC utilization at stroke discharge from Get with the Guidelines Stroke hospitals reached 17%, although age was inversely associated with DOAC use [6]. Data from the registry-based ORBIT-AF II study indicate DOAC use was lower in higher risk subgroups with a history of stroke or bleeding [28]. Underuse and subtherapeutic use of warfarin for secondary stroke prevention has been a historical problem, especially among the very old and those in nursing facilities [29–30]. DOACs require less monitoring than warfarin and no dietary restrictions, but the lack of evidence in older high risk patients, lack of a reversal agent (until idarucizumab, approved in 2015), drug interactions, and higher patient costs may impede use. Patient preferences regarding anticoagulation are heterogeneous and context dependent [31].

In our study, nearly half of patients received lower than standard doses. Among rivaroxaban users, 13% initiated the off-label 10mg dose and would be considered under-dosed for stroke prevention. A prior study of privately insured and Medicare Advantage patients observed 3% of rivaroxaban users were prescribed the 10mg dose [16]. Within the subgroup of DOAC users 80 years of age and without renal indications for dosage reductions, more than a third were prescribed less than standard dosages [16]. Although underdosing of apixaban was associated with an increased risk of stroke, dabigatran 75mg and rivaroxaban 10mg/15mg use in patients without a renal indication was not associated with differences in stroke or major bleeding rates [16]. A sub-therapeutic effect may be plausible for low dose rivaroxaban in our study, with an ischemic stroke rate well in excess of previous studies [8–9, 32–34]. Although we did not have laboratory values to estimate renal function and determine if dosing was appropriate, ischemic stroke and bleeding rates were low (0 events) among low dose rivaroxaban users with diagnosed CRI. Therefore, the elevated stroke rate among low dose rivaroxaban users was confined to patients without a diagnosis of CRI. In contrast, a supra-therapeutic effect may have been present in the low dose dabigatran group, which experienced a low stroke and high bleeding rate overall and in the subgroup with CRI. Dabigatran 75mg is indicated for patients with creatinine clearance 15–30 mL/min [35], although this dose was not evaluated in the RE-LY trial [17].

Multiple indirect comparisons from the RE-LY and ROCKET-AF phase III clinical trials reported comparable bleeding, stroke, and mortality risk between dabigatran and rivaroxaban for primary and secondary prevention of ischemic stroke [6–7]. In observational studies comparing the DOACs for primary prevention among Medicare beneficiaries, bleeding and mortality rates have generally favored dabigatran [8–9], including within subgroups of patients aged 75 years (75% of our cohort) and among patients with a CHADS₂ score >2 (99% of our cohort) [9]. In our post-stroke population, we found no association between treatment and death in the standard dose group, and observed a trend favoring rivaroxaban among patients receiving less than standard doses. Inconsistencies

between studies of real-world populations and indirect comparisons may be attributable in part to bias from inter-trial differences in sample characteristics (e.g., 87% CHADS₂ >2 in ROCKET-AF versus 33% in RE-LY) [17, 32], and to inherent differences between trial and real-world populations.

Our study was national in scope and focused on an understudied population initiating DOACs for secondary prevention. A new-user active-comparator design improved the internal validity of our findings, however, because data were only available for the early post-approval period (2011–2013) the sample size was modest. Because dabigatran 75mg is rarely used outside of the United States, international generalizability is limited. We did not have access to information about medication use during hospital and SNF stays. Clinical outcomes were operationalized using validated algorithms for hospital claims, thus minor adverse events that did not result in a hospitalization were not included. Concerns regarding unobserved confounding were mitigated in light of similarities in observed characteristics between treatment groups within dosing strata. The median duration of on-treatment follow-up was approximately 4 months, similar to previous research [9, 33].

In older adults with atrial fibrillation treated with DOACs following an ischemic stroke, results were inconclusive regarding the net clinical benefit of dabigatran versus rivaroxaban. Rates of ischemic stroke and bleeding events were higher in our study relative to estimates from a commercial and Medicare Supplemental insured population with previous stroke [33]. This may suggest that shifts in utilization patterns in response to even small relative differences in safety and effectiveness between anticoagulants could produce sizable reductions in the absolute number of events occurring in older high risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Stroke, bleeding, and death were more common in this study of older adults with atrial fibrillation using dabigatran or rivaroxaban post-stroke compared with prior studies of younger, healthier populations using these medications.
- Among patients that received less than standard dosages, rivaroxaban users had better clinical outcomes than dabigatran users, however, laboratory data were not available to determine whether less than standard doses were indicated.
- Among patients that received standard dosages, dabigatran users had better clinical outcomes than rivaroxaban users but further research is needed to confirm these preliminary findings.

Fig. 1.
12-Month Kaplan Meier Curves for the Composite Outcome for Dabigatran and Rivaroxaban, Stratified by Dosing

Fig. 2.
12-Month Kaplan Meier Curves for All-Cause Mortality for Dabigatran and Rivaroxaban,
Stratified by Dosing

Table 1.

Patient Characteristics by Anticoagulant and Dosage

	Less than Standard Dosage		Standard Dosage	
	Rivaroxaban 10 or 15 mg (n=205)	Dabigatran 75 mg (n=131)	Rivaroxaban 20 mg (n=173)	Dabigatran 150 mg (n=201)
Patient demographics				
Age in years, median (Q1, Q3)	87 (82, 90)	86 (83, 91)	82 (76, 86)	82 (77, 86)
Women, %	80.5	74.1	67.6	65.7
Baseline characteristics				
Nursing home residence, %	15.1	11.5	11.6	9.0
Hospitalization, %	6.8	8.4	4.1	9.0
# unique drug-dose combinations, median (Q1, Q3)	7 (4, 10)	7 (4, 10)	7 (4, 10)	6 (4, 9)
Select pre-index medications, ^a %				
Anticoagulant	15.1	8.4	17.9	19.9
Antiplatelet	21.0	15.3	15.6	11.4
Statin	65.4	66.4	73.4	64.7
Hospitalization Characteristics ^b				
Length of stay, median (Q1, Q3)	5 (3, 7)	5 (3, 6)	5 (3, 7)	5 (3, 7)
tPA, %	7.3	7.6	10.4	9.5
Ischemic stroke diagnosis				
Occlusion of precerebral artery ^c	2.4	1.5	4.2	2.5
Occlusion of cerebral artery ^d	97.6	98.5	95.8	97.5
Intracranial hemorrhage, %	2.9	3.1	7.5	2.0
Extracranial bleeding, %	2.0	2.3	5.2	3.5
Post-discharge Characteristics				
Inpatient rehabilitation admission, %	22.0	13.7	22.0	15.9
Time to index dispensing, median (Q1, Q3)	51 (28, 87)	46 (26, 70)	45 (27, 73)	45 (23, 70)
SNF length of stay, median (Q1, Q3)	42 (20, 98)	42 (20, 97)	34 (20, 77)	35 (18, 70)
Select Comorbidities, %				

	Less than Standard Dosage		Standard Dosage	
	Rivaroxaban 10 or 15 mg (n=205)	Dabigatran 75 mg (n=131)	Rivaroxaban 20 mg (n=173)	Dabigatran 150 mg (n=201)
Diabetes	26.3	27.5	28.3	32.8
Heart failure	21.0	27.5	21.4	19.9
Hypertension ^e	88.3	87.8	89.0	82.6
Chronic renal insufficiency ^b	24.4	29.8	14.4	9.3
CHADS ₂ Risk Score, %				
4	57.1	50.8	58.4	48.3
5 to 6	33.2	40.0	28.9	33.3
Cognitive skills at SNF entry, %				
Mildly impaired	30.2	27.5	22.0	29.4
Moderately to severely impaired	34.6	32.1	30.1	21.4
Bathel Index at SNF entry, median (Q1, Q3)	38 (28, 54)	38 (27, 51)	40 (26, 54)	41 (33, 55)

^aPre-index medications were measured during the baseline 90-day and the post hospital discharge pre-index period

^bIdentified during the index stroke hospitalization. Corresponds to an estimated glomerular filtration rate <60 ml/mi

^cICD-9 codes: 43301, 43311, 43321, 43331, 43381, 43391

^dICD-9 codes: 43401, 43411, 43491

^eMissing for 1 dabigatran low-dose user, imputed as present for this patient

Table 2.**Crude Outcome Incidence Rates by Anticoagulant and Dosage**

	Less than Standard Dose		Standard Dosage	
Description	Rivaroxaban 10 or 15 mg (n=205) ^a	Dabigatran 75 mg (n=131) ^b	Rivaroxaban 20 mg (n=173) ^c	Dabigatran 150 mg (n=201) ^d
Composite net clinical benefit outcome				
Crude incidence, per 100 pys	33.7	40.4	37.1	19.5
Number of events	30	28	27	23
Person-time at risk, years	89.0	69.3	72.8	118.1
All-cause mortality				
Crude incidence, per 100 pys	18.2	23.5	14.4	9.9
Number of events	17	17	11	12
Person-time at risk, years	93.6	72.3	76.2	121.2
Clinical events, incidence per 100 pys ^e				
Ischemic stroke	10.1	1.4	6.9	5.1
Bleeding (intra and extracranial)	3.4	11.5	8.2	3.4
AMI and VTE	2.2	2.9	1.4	1.7

^aComposite events: 15 deaths, 9 ischemic strokes, 1 TIAs, 1 ICH, 2 extracranial bleeds, 2 AMI, 0 VTE

^bComposite events: 16 deaths, 1 ischemic stroke, 1 TIAs, 1 ICH, 7 extracranial bleeds, 2 AMI, 0 VTE

^cComposite events: 10 deaths, 5 ischemic strokes, 5 TIAs, 0 ICHs, 6 extracranial bleeds, 0 AMI, 1 VTE

^dComposite events: 10 deaths, 6 ischemic strokes, 1 TIA, 0 ICHs, 4 extracranial bleeds, 2 AMI, 0 VTE

^eThe denominator was the person-time at risk for the composite outcome

Transient ischemic attack (TIA); intracranial hemorrhage (ICH); myocardial infarction (AMI); venous thromboembolism (VTE); person years (pys).

Table 3.

Unadjusted and Adjusted Hazard Ratios Comparing Dabigatran to Rivaroxaban within Dosage Strata for the Composite and All-Cause Mortality Outcomes

Outcome	Less than Standard Dose		Standard Dosage	
	Unadjusted HR	Adjusted HR ^a	Unadjusted HR	Adjusted HR ^a
Composite net clinical benefit outcome	1.37 (0.81–2.30)	1.48 (0.87–2.51)	0.65 (0.37–1.15)	0.65 (0.36–1.15)
All-cause mortality	1.54 (0.78–3.02)	1.67 (0.84–3.31)	0.95 (0.42–2.15)	1.05 (0.45–2.47)

^a Adjusted for age, sex, antiplatelet use, bleeding history, post-stroke rehabilitation stay, Barthel Index, cognitive impairment, CHADS₂

CI, confidence interval; HR, hazard ratio