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Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

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IMPORTANCE Dabigatran and rivaroxaban are non–vitamin K oral anticoagulants approved for stroke prevention in patients with nonvalvular atrial fibrillation (AF). There are no randomized head-to-head comparisons of these drugs for stroke, bleeding, or mortality outcomes.

OBJECTIVE To compare risks of thromboembolic stroke, intracranial hemorrhage (ICH), major extracranial bleeding including major gastrointestinal bleeding, and mortality in patients with nonvalvular AF who initiated dabigatran or rivaroxaban treatment for stroke prevention.

DESIGN, SETTING, AND PARTICIPANTS Retrospective new-user cohort study of 118 891 patients with nonvalvular AF who were 65 years or older, enrolled in fee-for-service Medicare, and who initiated treatment with dabigatran or rivaroxaban from November 4, 2011, through June 30, 2014. Differences in baseline characteristics were adjusted using stabilized inverse probability of treatment weights based on propensity scores. The data analysis was performed from May 7, 2015, through June 30, 2016.

EXPOSURES Dabigatran, 150 mg, twice daily; rivaroxaban, 20 mg, once daily.

MAIN OUTCOMES AND MEASURES Adjusted hazard ratios (HRs) for the primary outcomes of thromboembolic stroke, ICH, major extracranial bleeding including major gastrointestinal bleeding, and mortality, with dabigatran as reference. Adjusted incidence rate differences (AIRDs) were also estimated.

RESULTS A total of 52 240 dabigatran-treated and 66 651 rivaroxaban-treated patients (47% female) contributed 15 524 and 20 199 person-years of on-treatment follow-up, respectively, during which 2537 primary outcome events occurred. Rivaroxaban use was associated with a statistically nonsignificant reduction in thromboembolic stroke (HR, 0.81; 95% CI, 0.65-1.01; $P = .07$; AIRD = 1.8 fewer cases/1000 person-years), statistically significant increases in ICH (HR, 1.65; 95% CI, 1.20-2.26; $P = .002$; AIRD = 2.3 excess cases/1000 person-years) and major extracranial bleeding (HR, 1.48; 95% CI, 1.32-1.67; $P < .001$; AIRD = 13.0 excess cases/1000 person-years), including major gastrointestinal bleeding (HR, 1.40; 95% CI, 1.23-1.59; $P < .001$; AIRD = 9.4 excess cases/1000 person-years), and with a statistically nonsignificant increase in mortality (HR, 1.15; 95% CI, 1.00-1.32; $P = .051$; AIRD = 3.1 excess cases/1000 person-years). In patients 75 years or older or with $CHADS_2$ score greater than 2, rivaroxaban use was associated with significantly increased mortality compared with dabigatran use. The excess rate of ICH with rivaroxaban use exceeded its reduced rate of thromboembolic stroke.

CONCLUSIONS AND RELEVANCE Treatment with rivaroxaban 20 mg once daily was associated with statistically significant increases in ICH and major extracranial bleeding, including major gastrointestinal bleeding, compared with dabigatran 150 mg twice daily.

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Warfarin sodium, a vitamin K antagonist, has been a mainstay of therapy to reduce thromboembolic stroke risk in patients with atrial fibrillation (AF),[1-3] but it substantially increases the risk of intracranial and extracranial hemorrhage[3] and it can be difficult to maintain patients in the therapeutic range.[4] Dabigatran etexilate mesylate, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, are non–vitamin K antagonist oral anticoagulants (NOACs), which are simpler to dose than warfarin and do not require therapeutic monitoring.[5,6] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran treatment was superior to warfarin treatment for reduction of stroke and intracranial hemorrhage (ICH) in patients with nonvalvular AF but was inferior for major gastrointestinal bleeding, in which risk was increased.[7] In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), rivaroxaban treatment was noninferior to warfarin treatment for prevention of stroke or systemic embolization.[8] Intracranial and fatal bleeding events were reduced while major gastrointestinal bleeding was increased in the rivaroxaban arm.

Using data from RE-LY and ROCKET-AF, an indirect comparison reported that stroke and systemic embolization risk and hemorrhagic stroke risk were significantly reduced with dabigatran use compared with rivaroxaban use.[9] However, this analysis did not control for differences in baseline risk of future stroke or in the quality of warfarin anticoagulation between trials.[9,10] Another indirect comparison, restricted to the subset of patients from these trials at high risk of future stroke, found a statistically nonsignificant reduction in stroke or systemic embolization risk with dabigatran treatment.[10] The question remains unanswered whether these NOACs are therapeutically similar or whether clinically important differences exist that might lead prescribers and patients to prefer one over the other.

Given that 80% of patients with AF are 65 years or older,[11,12] we studied elderly Medicare beneficiaries with nonvalvular AF who initiated therapy with dabigatran or rivaroxaban and directly compared their risks of stroke, bleeding, and death. Both NOACs are available in the United States at 2 dosage levels for use in patients with nonvalvular AF, a lower dose for patients with impaired renal function and a standard dose for all other patients.[5,6] We compared patients initiating treatment with standard doses of dabigatran (150 mg twice daily) and rivaroxaban (20 mg once daily).

Key Points

Question How does rivaroxaban compare with dabigatran for stroke, bleeding, and mortality risks in patients with atrial fibrillation?

Findings In a new-user cohort study of 118 891 patients, rivaroxaban treatment was associated with significantly increased intracranial hemorrhage and major extracranial bleeding, including major gastrointestinal bleeding, and nonsignificantly reduced risk of thromboembolic stroke and increased risk of mortality. The absolute increase in intracranial hemorrhage with rivaroxaban treatment exceeded its reduced rate of thromboembolic stroke.

Meaning In this observational study, rivaroxaban use was associated with increased intracranial and major extracranial bleeding events compared with dabigatran use.

Methods

Study Population

Medicare provides health insurance coverage to persons aged 65 years and older and those younger than 65 years who have end-stage kidney disease or are disabled.[13,14] This study was restricted to elderly beneficiaries enrolled in fee-for-service Medicare Part A (hospitalization), Part B (outpatient medical care), and Part D (prescription drugs) because claims from these sources were necessary for research purposes. Patients enrolled in Medicare Advantage (Part C), which provides care through private insurance companies, were not included because claims for medical encounters and hospitalizations were not reliably captured by Medicare during the study period.

A new-user cohort design was used to compare patients initiating dabigatran or rivaroxaban at standard doses for treatment of nonvalvular AF.[15] We identified all patients with any inpatient or outpatient diagnoses of AF or atrial flutter, based on *International Classification of Diseases, Ninth Revision (ICD-9),* coding, who filled their first prescription for either drug from November 4, 2011, when rivaroxaban was approved for AF in the United States, through June 30, 2014. Patients were excluded if they had less than 6 months of enrollment in Medicare Parts A, B, and D, were younger than 65 years, had received prior treatment with warfarin or any NOAC, resided in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription (index date). Patients with a hospitalization extending beyond the index date were also excluded, as were kidney transplant recipients and patients undergoing dialysis. Additionally, we excluded patients with diagnoses indicating a potential alternative indication for anticoagulation in the 6 months preceding study entry (mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement). Because our purpose was to directly compare dabigatran and rivaroxaban, we did not include a warfarin-treated cohort.

This study was approved by the Research in Human Subjects Committee of the Center for Drug Evaluation and Research. Informed consent was not required due to the retrospective nature of the study.

Baseline Covariates

During the 6 months preceding cohort entry, Medicare claims data on chronic medical conditions, cardiovascular disease, risk factors for cardiovascular, stroke, and bleeding events, and health care utilization were collected for each patient, as were data on prescriptions for medications used for treatment of these disorders, as well as potentially interacting medications that could alter dabigatran or rivaroxaban pharmacokinetics. We also calculated the $CHADS_2$ score,[16] which predicts stroke risk in patients with AF and was used in RE-LY and

ROCKET-AF,[7,8] and the HAS-BLED score,[17] which predicts bleeding risk in patients with AF treated with warfarin.

Control for Confounding

To adjust for potential confounding due to baseline imbalances in study covariates while preserving sample size, we used inverse probability of treatment weighting (IPTW) based on the propensity score.[18-22] With this method, the propensity score (predicted probability of initiating dabigatran treatment given baseline characteristics) was used to generate patient-specific stabilized weights that control for covariate imbalances.[20,21] Covariate balance between the weighted cohorts was assessed using standardized mean differences.[22-24] A standardized difference of 0.1 or less indicates a negligible difference between groups.[22-24] The distributions of propensity scores and stabilized weights were inspected for outliers.

Cohort Follow-up

Follow-up began on the day after cohort entry and continued until disenrollment from Medicare, a gap in anticoagulant days of supply exceeding 3 days, a prescription fill for a different anticoagulant, kidney transplantation or initiation of dialysis, admission to a skilled nursing facility or nursing home, transfer to hospice care, end of the study period, or occurrence of a study outcome, whichever came first. We chose a 3-day gap allowance because of the short half-lives of dabigatran (12-17 hours) and rivaroxaban (11-13 hours in the elderly) and our desire to increase the likelihood that patients included in analyses were therapeutically anticoagulated.[5,6] We censored for admission to a skilled nursing facility or nursing home due to concerns about incomplete capture of outcomes in these settings, and for transfer to hospice care because most deaths in these patients were expected and therefore unlikely to be due to an acute, anticoagulant-associated event.

Study Outcomes

Primary outcomes were thromboembolic stroke, ICH, major extracranial bleeding events, including major gastrointestinal bleeding, and mortality. Secondary outcomes were all hospitalized extracranial bleeding events and acute myocardial infarction. Outcomes were defined using previously validated algorithms based on *ICD-9* diagnosis codes. These algorithms have reported positive predictive values ranging from 86% to 97% (eTable 1 in the Supplement).[25-35] Hospital records were not obtained to independently validate these outcomes. Major extracranial bleeding was defined as a fatal bleeding event, a hospitalized bleeding event requiring transfusion, or hospitalization with hemorrhage into an extracranial critical site (ie, intraspinal, intraarticular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome).[8,9] This definition differed from that in RE-LY and ROCKET-AF because we lacked data to document a decrease in hemoglobin concentration of at least 2 g/dL (to convert to grams per liter, multiply by 10.0) or the number of units transfused.[36] Mortality was ascertained by linkage to Social Security files, which provide the date, but not cause, of death and capture more than 95% of deaths for persons 65 years or older in the United States.[37] Our death outcome included deaths occurring as the first study outcome or within 30 days after hospitalization for another primary outcome event.

Statistical Analysis

All analyses were based on IPTW-adjusted cohorts and therefore accounted for potential confounding by baseline factors. Weighted Kaplan-Meier cumulative incidence plots were generated to characterize risk over time. Weighted Cox proportional hazards regression with robust estimation was used to estimate time-to-event in rivaroxaban compared with dabigatran (reference) cohorts. Adjusted incidence rate differences were estimated using weighted event counts and follow-up time within cohorts. Statistical significance was determined using 95% confidence intervals (CIs) and 2-tailed *P* values ($P \leq .05$). For all outcomes except mortality, the 30-day case fatality rate, defined as the number of deaths within 30 days of outcome occurrence divided by the total number of patients with that outcome, was determined.

Prespecified subgroup analyses were performed for all outcomes in categories defined by age, sex, hospitalization within the prior 30 days, concomitant use of antiplatelet agents, chronic kidney disease, and $CHADS_2$ and HAS-BLED scores. In a secondary analysis, Cox models were generated to examine risk during predefined intervals of time during therapy because bleeding risks may be greatest during the first 3 months after anticoagulant initiation.[29,38] We performed a number of sensitivity analyses. To assess whether the main analyses were affected by misclassification of exposed time, we restricted analysis to patients with at least 2 prescription fills of a study drug, and increased the gap allowance between anticoagulant prescriptions from 3 to 14 days. We repeated the main analysis using multivariable Cox regression, which included all covariates used in the weighted analysis. In post hoc sensitivity analyses, the CHA_2DS_2-VASc was substituted for the $CHADS_2$ score[39]; we no longer censored for initiation of dialysis or kidney transplantation, or admission to a nursing home, skilled nursing facility, or hospice; and we adjusted for the competing risks of death using the subdistribution of hazards approach.[40]

Analyses were performed using R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc).

Results

A total of 52 240 dabigatran and 66 651 rivaroxaban initiators contributed 15 524 and 20 199 person-years of on-treatment follow-up (mean [range] duration, 108 [0-969] and 111 [0-923] days), respectively. Before adjustment, there were minor differences in income status, geographic residence, emergency department visits in the prior 30 days, and prior use of injectable anticoagulants, antiplatelet agents, and digoxin. There were more substantial differences in prescriber specialty, with greater prescribing of rivaroxaban by cardiologists and less prescribing by family practitioners (**Table 1** and eTable 2 in the Supplement). After IPTW adjustment, the cohorts were well balanced across all covariates.

Table 1. Sociodemographic Factors, Medical Conditions, and Medication Use in Unweighted (Baseline) and Weighted (Adjusted) Cohorts of Medicare Beneficiaries Initiating Dabigatran or Rivaroxaban Treatment for Atrial Fibrillation From 2011 to 2014[a]

Characteristic	Unweighted Cohorts, %			Weighted Cohorts, %		
	Dabigatran (n = 52 240)	Rivaroxaban (n = 66 651)	SMD	Dabigatran (n = 52 264)[b]	Rivaroxaban (n = 66 630)[b]	SMD
Demographic						
Age, y						
65-74	50	51	0.02	50	50	0.00
75-84	40	40	0.00	40	40	0.00
≥85	10	9	0.03	9	9	0.00
Female sex	47	47	0.00	47	47	0.00
Race/ethnicity						
White	91	92	0.03	92	92	0.00
Black	4	3	0.02	4	4	0.00
Other	5	4	0.02	5	5	0.00
Medical History						
General						
Diabetes	34	32	0.03	33	33	0.00
Hypercholesterolemia	39	40	0.02	39	39	0.00
Hypertension	86	86	0.00	86	86	0.00
Kidney failure						
Acute	3	3	0.01	3	3	0.00
Chronic	10	8	0.04	9	9	0.00
Obesity	14	15	0.04	15	15	0.00
Peptic ulcer disease	<1	<1	0.01	<1	<1	0.00
Prior hospitalized bleeding event	<1	<1	0.00	<1	<1	0.00
Smoking	18	20	0.05	19	19	0.00
Cardiovascular Disease						
Acute myocardial infarction						
Past 1-30 d	1	1	0.03	1	1	0.00
Past 31-183 d	1	1	0.01	1	1	0.00
Coronary revascularization	14	15	0.02	15	15	0.00
Heart failure						
Hospitalized	3	3	0.01	3	3	0.00
Outpatient	13	11	0.04	12	12	0.00
Other ischemic heart disease	44	45	0.02	45	45	0.00
Stroke						
Past 1-30 d	2	2	0.00	2	2	0.00
Past 31-183 d	1	1	0.01	1	1	0.00
Other cerebrovascular disease	11	11	0.01	11	11	0.00
Transient ischemic attack	6	6	0.01	6	6	0.00
Cardioablation	2	2	0.00	2	2	0.00
Cardioversion	9	9	0.01	9	9	0.00
Other medical conditions						
Falls	5	5	0.00	5	5	0.00
Fractures	1	1	0.00	1	1	0.00
Syncope	8	9	0.02	9	9	0.00
Walker use	2	2	0.01	2	2	0.00
$CHADS_2$ score[c]						
0-1	33	34	0.03	34	34	0.00
2	40	40	0.02	40	40	0.00
3	19	18	0.01	19	19	0.00
≥4	8	8	0.00	8	8	0.00
HAS-BLED score[d]						
1	10	10	0.01	10	10	0.00
2	54	54	0.01	54	54	0.00
3	29	29	0.01	29	29	0.00
≥4	7	7	0.01	7	7	0.00

(continued)

Table 1. Sociodemographic Factors, Medical Conditions, and Medication Use in Unweighted (Baseline) and Weighted (Adjusted) Cohorts of Medicare Beneficiaries Initiating Dabigatran or Rivaroxaban Treatment for Atrial Fibrillation From 2011 to 2014[a] (continued)

Characteristic	Unweighted Cohorts			Weighted Cohorts		
	%			%		
	Dabigatran (n = 52 240)	Rivaroxaban (n = 66 651)	SMD	Dabigatran (n = 52 264)[b]	Rivaroxaban (n = 66 630)[b]	SMD
Medication Use						
General						
Estrogen therapy	2	2	0.01	2	2	0.00
Histamine H2 antagonists	5	5	0.00	5	5	0.00
Nonsteroidal anti-inflammatory drugs	14	14	0.01	14	14	0.00
Proton pump inhibitors	26	27	0.02	27	27	0.00
Selective serotonin reuptake inhibitor antidepressants	13	12	0.01	13	13	0.00
Cardiovascular						
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	59	58	0.01	59	58	0.00
Antiarrhythmics	25	25	0.01	25	25	0.00
Anticoagulants (injectable)	7	9	0.06	8	8	0.00
Antiplatelet	13	15	0.06	14	14	0.00
β-blockers	70	71	0.01	71	71	0.00
Calcium channel blockers	42	42	0.00	42	42	0.00
Digoxin	14	12	0.07	13	13	0.00
Diuretics						
Loop	25	22	0.05	23	23	0.00
Potassium sparing	8	8	0.02	8	8	0.00
Thiazide	30	30	0.00	30	30	0.00
Nitrates	9	9	0.01	9	9	0.00
Statins	58	57	0.00	57	57	0.00
Fibrates	5	4	0.02	4	4	0.00
Diabetes related						
Insulin	6	6	0.02	6	6	0.00
Metformin	15	15	0.01	15	15	0.00
Sulfonylureas	9	8	0.03	9	9	0.00
Other	6	6	0.03	6	6	0.00
Metabolic inhibitors[e]						
Amiodarone	9	10	0.01	9	9	0.00
Dronedarone	4	4	0.01	4	4	0.00
Azole antifungals	<1	<1	0.01	<1	<1	0.00
Prescriber specialty						
Cardiology	54	60	0.10	57	57	0.00
Family medicine	12	8	0.12	10	10	0.00
Internal medicine	21	19	0.04	20	20	0.00
Other	13	13	0.01	13	13	0.00

Abbreviation: SMD, standardized mean difference.

[a] Additional factors included in the inverse probability of treatment weighted model used for covariate adjustment are shown in eTable 2 in the Supplement.

[b] Weighted cohort sample size is calculated by summing the stabilized inverse probability of treatment weights from each patient in the cohort. The size of this fully adjusted pseudopopulation can differ slightly from that of the unadjusted actual population.

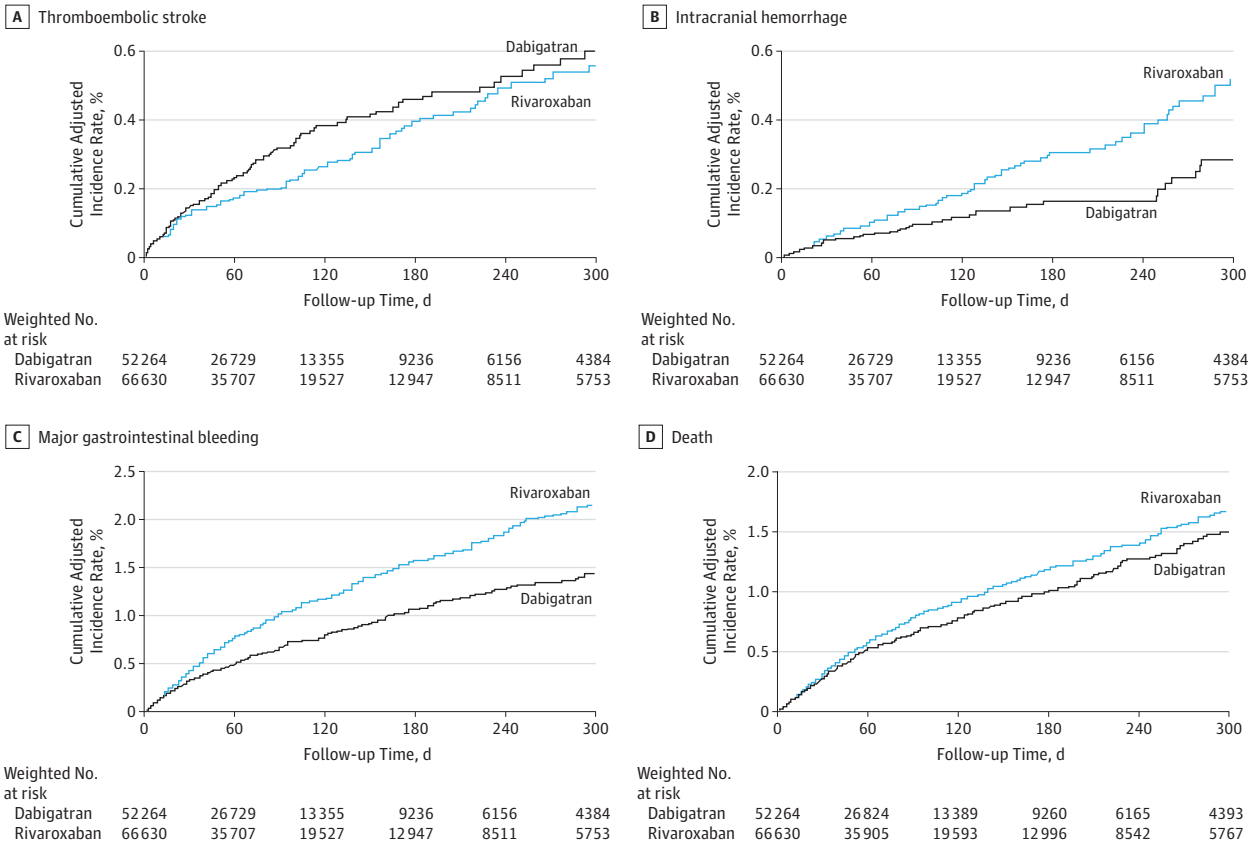
[c] The $CHADS_2$ score assigns points for the presence of congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, stroke, or transient ischemic attack.[16]

[d] The HAS-BLED score assigns points for the presence of hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio (INR), age 65 years or older, and antiplatelet drug or alcohol use.[17,18] Patients were not treated with warfarin and INR testing was not performed so labile INR was excluded from our scoring.

[e] Days supply of use overlapped with the date of first prescription for dabigatran or rivaroxaban.

During follow-up, there were 2537 primary outcome events including 306 thromboembolic strokes, 176 intracranial bleeding events, 1209 major extracranial bleeding events of which 1018 (84.2%) were gastrointestinal, and 846 deaths (724 as the first outcome and 122 within 30 days of another primary outcome event). Cumulative incidence plots showed early separation of event rates with continued divergence throughout follow-up for ICH, major gastrointestinal bleeding, and mortality, but convergence of event rates for thromboembolic stroke after day 240 (**Figure 1**). Rivaroxaban use was associated with a statistically nonsignificant decrease in thromboembolic stroke (hazard ratio [HR], 0.81; 95% CI,

Figure 1. Adjusted Kaplan-Meier Cumulative Incidence Plots of Thromboembolic Stroke, Intracranial Hemorrhage, Major Gastrointestinal Bleeding, and Death in Patients Treated With the Standard Dose of Dabigatran or Rivaroxaban for Stroke Prevention With Atrial Fibrillation



Note that the y-axis scales vary by outcome.

Table 2. Outcome Event Counts, Adjusted Incidence Rate Differences, and Crude and Adjusted Hazard Ratios Comparing Inverse Probability of Treatment-Weighted New-User Cohorts of Dabigatran and Rivaroxaban for Nonvalvular Atrial Fibrillation[a]

Outcome	Crude (Unadjusted) Incidence Rate per 1000 Person-years (No. of Events)		Adjusted Incidence Rate Difference per 1000 Person-years (95% CI)[b]	Hazard Ratio (95% CI)		*P* Value
	Dabigatran (n = 52 240)	Rivaroxaban (n = 66 651)		Crude	Adjusted	
Primary Outcomes						
Thromboembolic stroke	9.7 (150)	7.7 (156)	−1.8 (−3.8 to 0.1)	0.80 (0.64 to 1.00)	0.81 (0.65 to 1.01)	.07
Intracranial hemorrhage	3.7 (58)	5.8 (118)	2.3 (0.9 to 3.7)	1.58 (1.15 to 2.16)	1.65 (1.20 to 2.26)	.002
Major extracranial bleeding event	26.6 (413)	39.4 (796)	13.0 (9.2 to 16.7)	1.47 (1.31 to 1.66)	1.48 (1.32 to 1.67)	<.001
Gastrointestinal	23.3 (362)	32.5 (656)	9.4 (6.0 to 12.8)	1.39 (1.22 to 1.58)	1.40 (1.23 to 1.59)	<.001
Mortality	22.2 (346)	24.7 (500)	3.1 (−0.1 to 6.3)	1.12 (0.98 to 1.29)	1.15 (1.00 to 1.32)	.051
Secondary Outcomes						
All hospitalized extracranial bleeds	39.2 (608)	54.0 (1091)	15.1 (10.7 to 19.6)	1.38 (1.25 to 1.52)	1.39 (1.25 to 1.53)	<.001
Acute myocardial infarction	12.9 (200)	11.0 (223)	−1.7 (−4.0 to 0.6)	0.86 (0.71 to 1.05)	0.88 (0.72 to 1.06)	.18

[a] Dabigatran served as the reference group.

[b] Adjusted incidence rate difference = (rivaroxaban rate) − (dabigatran rate).

0.65-1.01; *P* = .07); statistically significant increases in ICH (HR, 1.65; 95% CI, 1.20-2.26; *P* = .002) and major extracranial bleeding (HR, 1.48; 95% CI, 1.32-1.67; *P* < .001), including major gastrointestinal bleeding (HR, 1.40; 95% CI, 1.23-1.59; *P* < .001); and with a statistically nonsignificant increase in mortality (HR, 1.15; 95% CI, 1.00-1.32; *P* = .051) (**Table 2**).

Results for the primary outcomes comparing the lower (renal) doses of rivaroxaban (15 mg once daily) vs dabigatran (75 mg twice daily) showed a similar pattern (eTable 3 in the Supplement). For secondary outcomes, there was a statistically significant increase in all hospitalized extracranial bleeding events with rivaroxaban and no difference in acute

myocardial infarction risk between drugs. Adjusted incidence rate differences were 1.8 fewer cases of thromboembolic stroke, 2.3 excess cases of ICH, 13.0 excess cases of major extracranial bleeding including 9.4 excess cases of major gastrointestinal bleeding, and 3.1 excess deaths per 1000 person-years with rivaroxaban treatment. The rate differences for thromboembolic stroke and mortality were not statistically significant. Of note, the increased rate of ICH with rivaroxaban treatment exceeded its decreased rate of thromboembolic stroke. The 30-day case fatality rates were 9.2% (thromboembolic stroke), 31.8% (ICH), 3.1% (major extracranial bleeding), 3.3% (major gastrointestinal bleeding), 2.7% (all hospitalized extracranial bleeding), and 9.7% (acute myocardial infarction), with little difference between cohorts.

Hazard ratios were generally consistent among subgroups with a few exceptions (**Figure 2**). For major gastrointestinal bleeding, the increased risk with rivaroxaban treatment diminished with increasing age, and for mortality, rivaroxaban risk was significantly increased in patients aged 75 years and older and in those with a $CHADS_2$ score greater than 2 (eTable 4 in the Supplement). The secondary analysis found no differences over time for any of the study outcomes except thromboembolic stroke, for which rivaroxaban risk may have been decreased during the first 90 days of use but not thereafter (HR, 0.71; 95% CI, 0.55-0.93 vs HR, 1.14; 95% CI, 0.74-1.75; *P* for interaction = .07) (eTable 5 in the Supplement). Sensitivity analyses yielded results similar to the main analysis (eTable 6 in the Supplement).

Discussion

In a direct comparison of patients with nonvalvular AF treated with standard doses of dabigatran or rivaroxaban, the risks of ICH and major extracranial bleeding, including major gastrointestinal bleeding, were significantly increased in patients treated with rivaroxaban. Although the risk of mortality was nonsignificantly increased with rivaroxaban across all age groups in the main analysis, it was significantly increased in patients aged 75 years or older or with $CHADS_2$ greater than 2, compared with dabigatran treatment. These latter results must be interpreted cautiously given that we examined multiple subgroups. Also, the net increase in ICH, the outcome with the highest case fatality rate, exceeded the net reduction in thromboembolic stroke for rivaroxaban treatment. Of note, in 2014, rivaroxaban was used 2 to 3 times more often than dabigatran in US patients with AF,[41] perhaps partly because of prescriber misperceptions about bleeding risks with dabigatran, arising from US Food and Drug Administration receipt of a large number of postmarketing case reports following its approval.[42] Ironically, we found substantially higher bleeding risks with use of rivaroxaban than dabigatran. Our results are consistent with a recently published small study from Denmark that reported no difference in stroke risk but increased bleeding and mortality risks with rivaroxaban 20 mg once daily compared with dabigatran 150 mg twice daily in patients with AF.[43]

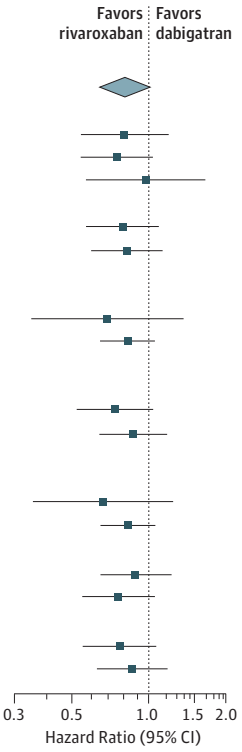
Our results differ from those based on indirect comparisons of clinical trials, which suggested that stroke risk might be higher with rivaroxaban use but with no difference in mortality or bleeding risks between the 2 NOACs.[9,10] This highlights the importance of head-to-head studies when evaluating comparative effectiveness of competing therapies. Indirect comparisons can be unreliable.[44] For example, rivaroxaban-treated patients in ROCKET-AF were older and had higher baseline $CHADS_2$ scores than dabigatran-treated patients in RE-LY while time in therapeutic range for warfarin-treated patients in RE-LY was greater than in ROCKET-AF.[9,10,44] These differences, and perhaps others not measured, could confound an indirect comparison. Whereas a randomized direct comparison between dabigatran and rivaroxaban would be optimal, such a study is unlikely to be undertaken by the manufacturer of either product.

Our findings suggest that standard-dose rivaroxaban produced a greater anticoagulant effect than standard-dose dabigatran. While plasma half-lives of dabigatran and rivaroxaban are each approximately 12 hours, dabigatran is dosed twice daily and rivaroxaban only once daily.[5,6] Once-daily dosing of rivaroxaban would be expected to achieve higher peak and lower trough serum concentrations than twice-daily administration of the same total daily dose.[45] Reduction of the once-daily dose or adoption of a twice-daily regimen might reduce the excess bleeding and subgroup mortality risks that we observed. However, effects of such dose adjustment on both thrombotic and bleeding events would need to be evaluated through clinical testing. It is also possible that our results arose because some patients taking dabigatran did so only once daily rather than twice daily, leading to dabigatran-treated patients being inadequately anticoagulated. We believe that this is unlikely for 2 reasons. In a previous study of patients with AF initiating warfarin or standard-dose dabigatran treatment, using the same Medicare database and outcome definitions as in this study, results similar to those of the RE-LY trial were obtained, suggesting that adherence to the twice-daily dabigatran regimen by Medicare beneficiaries was comparable to that of patients in RE-LY.[38] Also, our sensitivity analysis restricted to patients filling 2 or more NOAC prescriptions yielded results similar to the primary analysis. This analysis included only dabigatran-treated patients who filled their second prescription by the date expected had they been taking it twice daily. Patients taking dabigatran once daily would not be expected to fill their second prescription by this date because they would still have a large remaining medication supply. Finally, the lower dose of dabigatran is recommended for patients with a creatinine clearance (CrCl) of 15 to 30 mL/min/1.73 m^2, whereas for rivaroxaban, it is a broader range of 15 to 50 mL/min/1.73 m^2 (to convert to milliliters per second per square meter, multiply by 0.0167).[5,6] In our standard-dose analysis, we excluded patients treated with the lower dose. We cannot exclude the possibility that a higher proportion of rivaroxaban-treated patients with renal impairment were treated off-label with the standard dose because of the broader CrCl range guiding rivaroxaban dosing. If this occurred, a greater anticoagulant effect with rivaroxaban might be observed in our data. Medicare claims do not capture CrCl or other laboratory

Figure 2. Subgroup-Specific Adjusted Hazard Ratios With 95% Confidence Intervals for Thromboembolic Stroke, Intracranial Hemorrhage, Major Gastrointestinal Bleeding, and Death/Mortality in Elderly Patients With Atrial Fibrillation Treated With the Standard Dose of Dabigatran or Rivaroxaban

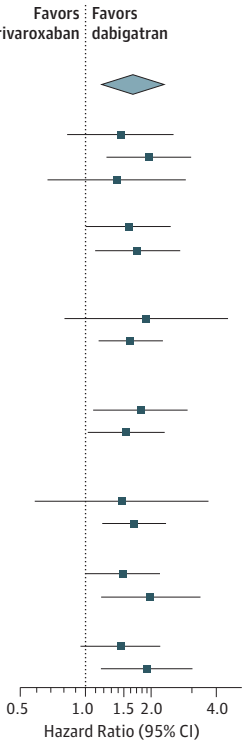
A Thromboembolic stroke

Parameter	No. of Events (1000 Person-years) Dabigatran	Rivaroxaban
Overall	150 (15.5)	156 (20.2)
Age, y		
65-74	49 (7.8)	50 (10.5)
75-84	75 (6.4)	76 (8.1)
>85	26 (1.4)	30 (1.7)
Sex		
Male	74 (8.1)	77 (10.5)
Female	76 (7.4)	79 (9.7)
Chronic Kidney Disease		
Yes	20 (1.3)	15 (1.4)
No	130 (14.2)	141 (18.8)
Recent Hospitalization		
Yes	65 (4.1)	68 (5.8)
No	85 (11.4)	88 (14.4)
Prescription Antiplatelet Use		
Yes	20 (1.5)	21 (2.2)
No	130 (14.1)	135 (18.0)
$CHADS_2$ Score		
≤2	73 (11.5)	82 (15.1)
>2	77 (4.1)	74 (5.1)
HAS-BLED Score		
≤2	75 (10.2)	73 (13.3)
>2	75 (5.3)	83 (6.9)



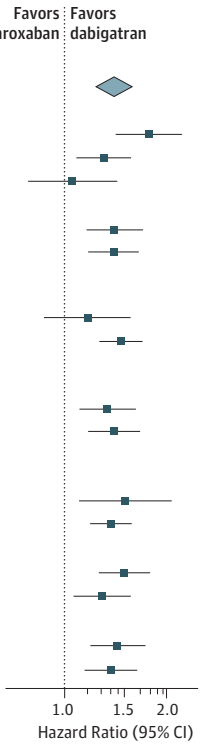
B Intracranial hemorrhage

Parameter	No. of Events (1000 Person-years) Dabigatran	Rivaroxaban
Overall	58 (15.5)	118 (20.2)
Age, y		
65-74	19 (7.8)	36 (10.5)
75-84	27 (6.4)	65 (8.1)
>85	12 (1.4)	17 (1.7)
Sex		
Male	29 (8.1)	58 (10.5)
Female	29 (7.4)	60 (9.7)
Chronic Kidney Disease		
Yes	8 (1.3)	15 (1.4)
No	50 (14.2)	103 (18.8)
Recent Hospitalization		
Yes	22 (4.1)	53 (5.8)
No	36 (11.4)	65 (14.4)
Prescription Antiplatelet Use		
Yes	7 (1.5)	16 (2.2)
No	51 (14.1)	102 (18.0)
$CHADS_2$ Score		
≤2	39 (11.5)	75 (15.1)
>2	19 (4.1)	43 (5.1)
HAS-BLED Score		
≤2	34 (10.2)	61 (13.3)
>2	24 (5.3)	57 (6.9)



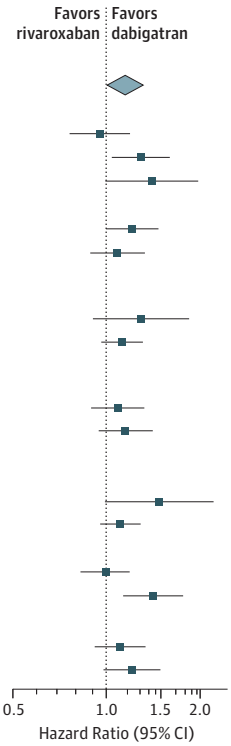
C Major gastrointestinal bleeding

Parameter	No. of Events (1000 Person-years) Dabigatran	Rivaroxaban
Overall	362 (15.5)	656 (20.2)
Age, y		
65-74	109 (7.8)	259 (10.5)
75-84	177 (6.4)	295 (8.1)
>85	76 (1.4)	102 (1.7)
Sex		
Male	161 (8.1)	298 (10.5)
Female	201 (7.4)	358 (9.7)
Chronic Kidney Disease		
Yes	81 (1.3)	102 (1.4)
No	281 (14.2)	554 (18.8)
Recent Hospitalization		
Yes	159 (4.1)	311 (5.8)
No	203 (11.4)	345 (14.4)
Prescription Antiplatelet Use		
Yes	58 (1.5)	136 (2.2)
No	304 (14.1)	520 (18.0)
$CHADS_2$ Score		
≤2	196 (11.5)	387 (15.1)
>2	166 (4.1)	269 (5.1)
HAS-BLED Score		
≤2	172 (10.2)	325 (13.3)
>2	190 (5.3)	331 (6.9)



D Mortality

Parameter	No. of Events (1000 Person-years) Dabigatran	Rivaroxaban
Overall	346 (15.6)	500 (20.3)
Age, y		
65-74	145 (7.8)	180 (10.5)
75-84	145 (6.4)	232 (8.1)
>85	55 (1.4)	88 (1.7)
Sex		
Male	178 (8.2)	276 (10.5)
Female	168 (7.4)	224 (9.7)
Chronic Kidney Disease		
Yes	55 (1.3)	77 (1.4)
No	291 (14.2)	423 (18.9)
Recent Hospitalization		
Yes	161 (4.1)	259 (5.8)
No	185 (11.4)	241 (14.4)
Prescription Antiplatelet Use		
Yes	36 (1.5)	81 (2.2)
No	310 (14.1)	419 (18.0)
$CHADS_2$ Score		
≤2	219 (11.5)	276 (15.2)
>2	127 (4.1)	224 (5.1)
HAS-BLED Score		
≤2	193 (10.2)	270 (13.3)
>2	153 (5.4)	230 (7.0)



Dabigatran served as the reference group.

results so we cannot definitively evaluate this. With a broader CrCl range, we would expect a higher proportion of rivaroxaban than dabigatran users to be treated with the lower dose, which was present in our data, with 19.6% of dabigatran- and 26.8% of rivaroxaban-treated patients treated with the renal dose (eTable 7 in the Supplement).

This study had several limitations. The mean duration of on-treatment follow-up was less than 4 months, thereby reducing sample size at longer durations of use. Other studies of NOAC safety using other US databases have had mean follow-up shorter than 6 months, indicating a limited capacity to study longer-term risks.[46-48] Despite this, we had a larger number of patients still receiving therapy at 6 or 8 months than the number who started NOAC therapy in these and other studies.[43,46-49] This study was observational and may be subject to residual confounding by unmeasured factors. This could lead to biased estimates of risk. Also, our study was restricted to patients aged 65 years or older, the age group accounting for 80% of patients with AF. The comparative effects of dabigatran and rivaroxaban treatment could be different in younger populations. Finally, our study examined warfarin-naive first-time users of dabigatran or rivaroxaban for stroke prevention in AF. Results could differ in patients switching from warfarin to a NOAC.

Conclusions

In this large direct comparison of patients with AF treated with dabigatran or rivaroxaban, rivaroxaban use was associated with statistically significant increases in the risk of ICH and major extracranial bleeding, including major gastrointestinal bleeding, and possibly with increased mortality in older patients or those with higher baseline risk of stroke. The greater anticoagulant effect observed with rivaroxaban treatment may be due to the higher dose required for once-daily dosing. A contribution to this effect by off-label use of standard-dose rivaroxaban in patients with impaired renal function cannot be excluded.

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