Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack

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Background and Purpose—Limited real-world data exist comparing each non–vitamin K antagonist oral anticoagulant (NOAC) to warfarin in patients with nonvalvular atrial fibrillation who have had a previous ischemic stroke or transient ischemic attack.

Methods—Using MarketScan claims from January 2012 to June 2015, we identified adults newly initiated on oral anticoagulation, with ≥2 diagnosis codes for nonvalvular atrial fibrillation, a history of previous ischemic stroke/transient ischemic attack, and ≥180 days of continuous medical and prescription benefits before anticoagulation initiation. Three analyses were performed comparing 1:1 propensity score–matched cohorts of apixaban versus warfarin (n=2514), dabigatran versus warfarin (n=1962), and rivaroxaban versus warfarin (n=5208). Patients were followed until occurrence of a combined end point of ischemic stroke and intracranial hemorrhage (ICH) or major bleed, switch/discontinuation of index oral anticoagulation, insurance disenrollment, or end of follow-up. Mean follow-up was 0.5 to 0.6 years for all matched cohorts.

Results—Using Cox regression, neither apixaban nor dabigatran reduced the combined primary end point of ischemic stroke or ICH (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.33–1.48 and HR, 0.53; 95% CI, 0.26–1.07) and had nonsignificant effect on hazards of major bleeding (HR, 0.79; 95% CI, 0.38–1.64 and HR, 0.58; 95% CI, 0.26–1.27) versus warfarin. Rivaroxaban reduced the combined end point of ischemic stroke or ICH (HR, 0.45; 95% CI, 0.29–0.72) without an effect on major bleeding (HR, 1.07; 95% CI, 0.71–1.61). ICH occurred at rates of 0.16 to 0.61 events per 100 person-years in the 3 NOAC analyses, with no significant difference for any NOAC versus warfarin.

Conclusions—Results from our study of the 3 NOACs versus warfarin in nonvalvular atrial fibrillation patients with a previous history of stroke/transient ischemic attack are relatively consistent with their respective phase III trials and previous stroke/transient ischemic attack subgroup analyses. All NOACs seemed no worse than warfarin in respect to ischemic stroke, ICH, or major bleeding risk. **(*Stroke*. 2017;48:2142-2149. DOI: 10.1161/STROKEAHA.117.017474.)**

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

Nonvalvular atrial fibrillation (NVAF) patients who have had a previous ischemic stroke or transient ischemic attack (TIA) are at an increased risk of recurrent stroke and major bleeding.[1] Each of the pivotal randomized controlled trials (RCTs) comparing apixaban, dabigatran, or rivaroxaban to warfarin performed subgroup analyses of patients with or without a previous history of stroke or TIA.[2–4] These subgroup analyses found no statistically significant interactions for efficacy or safety end points between patients with or without a previous history of stroke/TIA for each of the individual non–vitamin K antagonist oral anticoagulants (NOACs) versus warfarin. However, the extent to which these RCT-based subgroup results apply to routine clinical practice is unclear. Moreover, there is a relative paucity of real-world evidence evaluating both the effectiveness and safety of NOACs in NVAF patients with a previous history of stroke or TIA.

Large administrative claims database analyses, while insufficient for demonstrating causal relationships, can provide valuable insight into anticoagulants' effectiveness and safety

Received March 25, 2017; final revision received May 25, 2017; accepted June 5, 2017.

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Presented in part at the American College of Cardiology 66th Scientific Session and Expo, Washington, DC, March 17–19, 2017.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.017474/-/DC1.

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in a routine clinical practice. We sought to evaluate the real-world effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in NVAF patients with a previous history of ischemic stroke/TIA.

Methods

We performed REAFFIRM (Effectiveness and Safety of Apixaban, Dabigatran and Rivaroxaban Versus Warfarin in Patients with Nonvalvular Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack), a retrospective claims database study using US Truven MarketScan data from January 2012 to June 2015. MarketScan combines 2 separate databases, a commercial database and the Medicare supplemental database, to cover all age groups, and contains claims from 100 employers, health plans, and government and public organizations representing about 170 million covered lives in the United States.[5] MarketScan captures health plan enrollment records, participant demographics, International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes, procedure codes, admission and discharge dates, inpatient mortality data, outpatient medical services data, and prescription dispensing records. All data included in the MarketScan databases are deidentified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. For this reason, this study was exempt from institutional review board oversight.

To be included in this study, patients had to be oral anticoagulant naive during the 180 days before the day of the first qualifying oral anticoagulant dispensing (index date), newly initiated on apixaban, dabigatran, rivaroxaban, or warfarin, ≥18 years of age on the index date, with a history of previous ischemic stroke or TIA, ≥2 International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for atrial fibrillation (online-only Data Supplement) without codes suggesting valvular heart disease, and ≥180 days of continuous medical and prescription coverage before initiation of oral anticoagulation (which serves as the study's baseline period). Patients with a transient cause of NVAF, venous thromboembolism, hip or knee arthroplasty, malignant cancer or pregnancy, and patients prescribed >1 oral anticoagulant on the index date or during follow-up were excluded. We included apixaban, dabigatran, and rivaroxaban patients starting at each NOACs' individual US Food and Drug Administration approval date (December 2012 for apixaban, October 2010 for dabigatran, and November 2011 for rivaroxaban) and only matched NOAC to warfarin users initiating anticoagulation during a corresponding time frame.

Propensity scores were calculated using multivariable logistic regression incorporating frequently used variables and potential risk factors for differential oral anticoagulant exposure in Table,[1,6–11] including patient demographics (age 65–74, ≥65 years and sex), comorbidities, concomitant nonoral anticoagulant medications, individual components of the CHADS2, CHA2DS2-VASc and modified HASBLED risk stratification scores and modified SAMe-TT2R2 (≥3), and Charlson Comorbidity Index (2–3, ≥4) measured during the 180-day index period. Each eligible apixaban, dabigatran, and rivaroxaban user was 1:1 propensity score matched (using greedy nearest-neighbor matching without replacement and a caliper of 1%) to a warfarin user to minimize the presence of baseline differences between cohorts. Thus, 3 statistically independent analyses were performed comparing 1:1 propensity score–matched cohorts of apixaban:warfarin, dabigatran:warfarin, and rivaroxaban:warfarin. Residual differences in characteristics between matched cohorts were assessed by calculating standardized differences between cohorts (<10% considered well balanced).[12]

The primary effectiveness end point for this study was a combined end point of ischemic stroke or intracranial hemorrhage (ICH; including intracerebral, subarachnoid, and other ICH). Although this is not the primary end point in the typical stroke prevention RCT which focuses on ischemic and hemorrhagic stroke,[2–4] the ability to differentiate between hemorrhagic strokes and other types of ICH is challenging when relying on International Classification of Diseases, Ninth Revision, Clinical Modification coding only as many ICH events are coded as unspecified ICH (432.9). Moreover, this combined end point of ischemic stroke or ICH is the a priori primary end point in the US Food and Drug Administration Mini-Sentinel postmarketing surveillance protocol.[6] Although composite end points can simplify risk–benefit assessment, it is possible that the stroke prevention effectiveness could come at the cost of increased bleeding risk. For this reason, we also assessed ischemic stroke and ICH separately as secondary end points. Major bleeding was our primary safety end point. The occurrence of the ischemic stroke and ICH end points during the observation period was determined by the presence of an appropriate International Classification of Diseases, Ninth Revision, Clinical Modification discharge diagnosis code according to the Mini-Sentinel protocol (primary position for ischemic stroke, primary or secondary positions for ICH).[6] Major bleeding was determined based on codes previously used by Yao et al[7] in the primary or secondary code positions. Patients were followed until the occurrence of an ischemic stroke, ICH or other major bleed, switch or discontinuation of oral anticoagulant therapy, leaving the insurance plan or end of study follow-up (an on-treatment approach). Patients were considered to have discontinued oral anticoagulant therapy if a gap ≥14 days was detected between the most recent anticoagulant fill date and the date when there were no days of anticoagulant supply anticipated to be remaining.

Baseline patient characteristics were analyzed using descriptive statistics. The incidence of primary and secondary study end points was reported as the number of events per 100 person-years anticoagulant exposure and calculated as the number of patients with ≥1 documented event divided by each respective cohorts' time at risk. Cox proportional hazards regression was performed on the matched cohorts and results reported as hazard ratios (HRs) and 95% confidence intervals. Because all baseline characteristics were balanced after propensity score matching, the regression analysis included only oral anticoagulant treatment as an independent variable. We performed analyses to examine the impact of NOAC dosing on their effectiveness and safety (versus warfarin) whereby we restricted inclusion to NOAC patients receiving the standard (high) dose only (apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily) and repropensity score matched them to warfarin patients. We also performed a sensitivity analysis in which we randomly (using statistical software to select patients) identified 981 patients receiving each NOAC (representing the sample size of the smallest NOAC group; dabigatran) and separately 1:1 propensity score matched each to a warfarin user (ie, shrunken cohort analysis). These analyses were performed on the study's primary effectiveness and safety end points. Statistical analyses were performed using SAS version 9.4 (SAS Inc, Cary, NC) and IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY). In all cases, a P value <0.05 was considered significant. This article was written in compliance with the STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology).[13]

Results

Three independent matched cohorts of NVAF patients (apixaban versus warfarin, n=2514; dabigatran versus warfarin, n=1962; and rivaroxaban versus warfarin, n=5208) whom experienced a previous ischemic stroke or TIA were created (Figure 1). On the basis of the assessment of standardized differences for each NOAC to warfarin cohort, patients were deemed well balanced (<10% difference) on all independent variables entered into the propensity score logistic regression model for all 3 analyses. The baseline characteristics of each NOAC:warfarin-matched cohort are depicted in Table. The mean±SD duration of follow-up was 0.5±0.5, 0.6±0.6, and 0.6±0.6 years for the apixaban-, dabigatran-, and rivaroxaban-matched cohorts, respectively. Median (interquartile range) duration of follow-up was 0.3 (interquartile range, 0.1–0.7), 0.3 (interquartile range, 0.2–0.8), and 0.4 (interquartile range, 0.2–0.8) for the apixaban-, dabigatran-, and rivaroxaban-matched cohorts.

Table. Baseline Characteristics in Propensity Score–Matched NOAC and Warfarin Users

Variable	Apixaban, n=1257 (%)	Warfarin, n=1257 (%)	Dabigatran, n=981 (%)	Warfarin, n=981 (%)	Rivaroxaban, n=2604 (%)	Warfarin, n=2604 (%)
Demographics						
Age, y, median (IQR)*	74 (63, 82)	74 (63, 82)	73 (63, 80)	73 (64, 82)	72 (63, 81)	73 (63, 82)
18–64	31.5	29.3	29.4	26.8	29.9	28.5
65–74	20.8	21.7	27.6	27.7	25.1	25.2
≥75	47.7	49.0	43.1	45.5	45.0	46.2
Male sex	54.0	55.8	51.8	52.3	53.1	53.7
Comorbidities						
Hypertension	84.2	83.4	73,2	75.3	76.9	76.5
Diabetes mellitus	33.4	34.1	32.8	32.1	32.5	32.3
Heart failure	19.6	18.8	18.0	17.9	18.6	18.2
Vascular disease	20.7	20.6	18.2	16.8	21.5	20.7
Pulmonary disease	18.7	18.2	19.8	17.6	20.2	19.4
Any renal disease	11.5	12.0	9.5	8.7	9.4	9.3
End-stage renal disease	0.2	0.6	0.0	0.0	0.0	0.3
Liver disease	3.1	3.3	1.9	1.8	2.5	2.6
History of major bleeding	6.1	6.0	3.8	2.8	4.6	4.9
Alcohol abuse	2.1	2.0	1.2	0.9	1.7	1.7
Smoker	8.7	7.7	6.7	6.9	7.6	7.6
Obesity	12.9	13.2	8.8	7.8	11.0	11.4
Medication use						
Antiplatelets or NSAIDs	35.4	36.0	31.7	31.2	35.1	35.1
ACE inhibitors or ARBs	53.5	55.7	50.6	49.1	50.9	49.7
β-blockers	60.6	60.9	58.7	56.8	56.2	56.5
Diltiazem	11.2	11.9	10.3	10.0	8.9	8.7
Verapamil	2.1	1.8	2.3	1.6	2.1	2.4
Other calcium channel blockers	25.8	26.2	21.4	21.5	25.2	24.9
Diuretics	31.5	31.3	32.0	32.2	31.3	31.3
Digoxin	4.6	4.5	7.8	8.3	5.9	6.1
Amiodarone	4.8	5.0	3.6	3.1	3.4	3.0
Dronedarone	1.5	1.6	1.6	1.7	1.5	1.3
Other antiarrhythmic drugs	5.1	4.1	5.2	4.6	3.8	4.0
Statin	61.3	62.6	55.2	55.0	57.9	57.8
Other cholesterol lowering drugs	11.8	11.9	12.7	12.1	12.1	11.8
Metformin	14.6	14.3	13.4	12.4	13.0	13.7
Sulfonylureas	8.0	8.2	10.2	9.5	8.0	8.1
Thiazolidinedione	1.7	1.8	1.8	1.7	1.7	1.5
Insulin	9.1	8.7	8.8	8.2	8.4	8.8
Other diabetes mellitus drugs	6.0	5.3	4.9	4.2	5.1	5.3
Antidepressants	24.3	23.9	21.5	21.4	22.7	22.6
Antiulcer drugs	24.6	24.1	20.9	20.3	23.3	23.1

(*Continued*)

Table. Continued

Variable	Apixaban, n=1257 (%)	Warfarin, n=1257 (%)	Dabigatran, n=981 (%)	Warfarin, n=981 (%)	Rivaroxaban, n=2604 (%)	Warfarin, n=2604 (%)
Risk stratification scores						
CHADS2*†						
Median (IQR)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)
2–3	37.5	36.9	45.6	44.0	43.1	43.3
≥4	62.5	63.1	54.4	56.0	56.9	56.7
CHA2DS2-VASc*‡						
Median (IQR)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)
2–3	13.4	13.5	15.7	14.8	15.9	16.1
≥4	86.6	86.5	84.3	85.2	84.1	83.9
Modified HASBLED*§						
Median (IQR)	4 (4, 5)	4 (4, 5)	3 (3, 4)	3 (3, 4)	3 (4, 5)	3 (4, 5)
≥3	95.7	95.4	93.8	95.4	94.3	94.4
Modified SAMe-TT2R2‖						
Median (IQR)	2 (1, 2)	2 (1, 2)	2 (1, 2)	2 (1, 2)	2 (1, 2)	2 (1, 2)
≥3	16.7	14.9	12.6	12.6	14.2	13.5
Charlson Comorbidity Index¶						
Median (IQR)	3 (3, 4)	3 (3, 4)	3 (2, 4)	3 (2, 4)	3 (3, 4)	3 (3, 4)
2–3	55.3	56.6	60.9	61.5	57.5	57.1
≥4	44.7	43.4	39.1	38.5	42.5	42.9

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; NOAC, non–vitamin K antagonist oral anticoagulant; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*Mean age and CHADS2, CHA2DS2-VASc, and modified HASBLED risk scores were not included in the propensity score model; instead age as categories (18–64, 65–74, ≥75 y) individual components CHADS2, CHA2DS2-VASc, and Modified HASBLED were used.

†CHADS2=congestive heart failure, 1 point; hypertension, 1 point; age ≥75 y, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischemic attack, 2 points.

‡CHA2DS2-VASc=congestive heart failure, 1 point; hypertension, 1 point; age ≥75 y, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; age 65–74 y, 1 point; female sex, 1 point.

§Modified HASBLED=hypertension, 1 point; age >65 y, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

‖Modified SAMe-TT2R2=female sex, 1 point; age <60 y, 1 point; medical history (2 of the following: hypertension, diabetes mellitus, myocardial infarction, peripheral artery disease, congestive heart failure, history of stroke, pulmonary disease, hepatic, or renal disease), 1 point; treatment interacting medications (eg, amiodarone), 1 point; tobacco use, 2 points; race (non-white), not assessed

¶Charlson Comorbidity Index=myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes mellitus, 1 point each; hemiplegia, moderate or severe kidney disease, diabetes mellitus with end-organ damage, tumor, leukemia, lymphoma, 2 points each; moderate or severe liver disease, 3 points each; malignant tumor, metastasis, acquired immune deficiency syndrome, 6 points each.

After Cox proportion hazard regression, both apixaban and dabigatran were found to nonsignificantly reduce patients' hazard versus warfarin of the combined end point of ischemic stroke or ICH by 30% and 47%, respectively, with no significant difference in major bleeding risk (Figure 2). Rivaroxaban significantly reduced ischemic stroke/ICH hazard by 55% (P=0.001) and had no statistically significant effect on major bleeding. Ischemic stroke risk was not significantly reduced by apixaban or dabigatran (P≥0.18), but was reduced with rivaroxaban (52%). ICH occurrence was not significantly different with each NOAC versus warfarin.

A total of 20.8%, 17.7%, and 26.2% of apixaban, dabigatran, and rivaroxaban patients received the reduced dose (<5 mg twice daily of apixaban, <150 mg twice daily of dabigatran, or <20 mg once daily of rivaroxaban). On analysis restricted to the standard dose of each NOAC compared with warfarin, no substantial difference was observed in regard to the primary effectiveness or safety end point for any NOAC versus warfarin (HRs for the combined end point of ischemic stroke or ICH=0.85, 0.73, and 0.30 for apixaban, dabigatran, and rivaroxaban; HRs=0.64, 0.63, and 1.10 for the major bleeding end point for apixaban, dabigatran, and rivaroxaban, respectively) compared with the main analysis (Figure 3). The shrunken cohort sensitivity analysis also provided results consistent with the overall study findings, albeit with wider 95% confidence intervals (Figure 4).

Discussion

This study in the US MarketScan administrative claims databases evaluated NVAF patients who had a previous ischemic stroke or TIA. Our analysis demonstrated that apixaban and

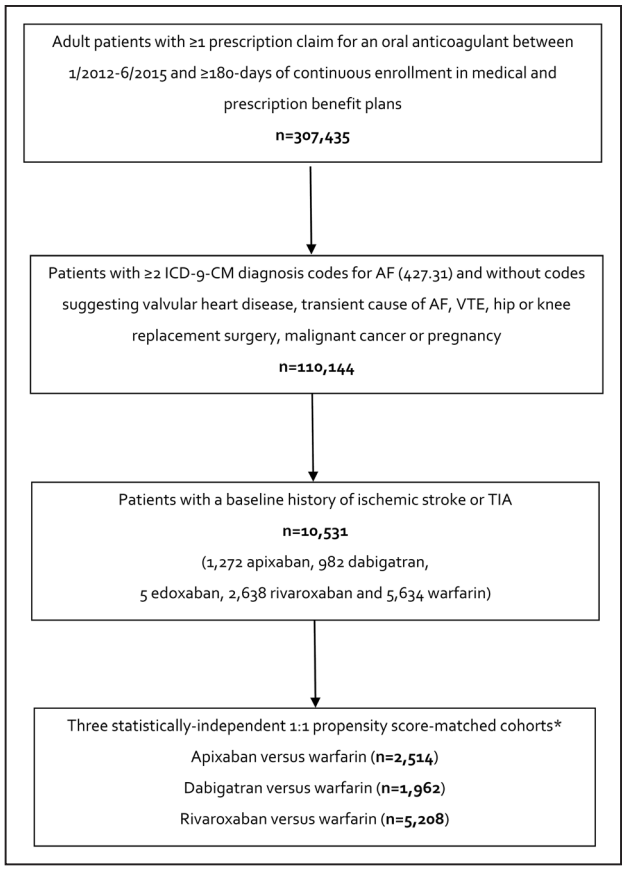

Figure 1. Patient inclusion and exclusion. AF indicates atrial fibrillation; ICD-9-CM, International Classification of Diseases-Ninth Revision-Clinical Modification; TIA, transient ischemic attack; and VTE, venous thromboembolism. *We did not perform an edoxaban:warfarin match because of the small edoxaban sample size.

dabigatran nonsignificantly reduced patients' hazard of developing the primary combined end point of ischemic stroke or ICH and had a negligible effect on the risk of major bleeding compared with warfarin. Neither dabigatran nor apixaban significantly reduced ischemic stroke versus warfarin. The most frequently used NOAC for NVAF patients with a history of ischemic stroke/TIA in this analysis was rivaroxaban. Rivaroxaban was shown to significantly reduce the hazard of the combined end point of ischemic stroke or ICH and ischemic stroke alone by 55% and 52%, respectively, versus warfarin, without increasing major bleeding risk. As anticipated based on RCT findings, ICH occurrence was not significantly different with any NOAC versus warfarin. Our analyses restricted to each NOAC standard dose versus warfarin showed results consistent with the overall analysis; however, because of our inability to determine whether patients were receiving the standard or reduced dose of each NOAC in accordance with its product labeling, we suggest cautious interpretation of the latter findings.

In the RCTs comparing each NOAC to warfarin, subgroup analyses of patients with or without a previous history of stroke/TIA were performed,[2–4] and no statistically significant interaction between subgroups was seen for any NOAC versus warfarin for the end points of any stroke (*P* values for interaction ≥0.16 for all), ischemic (or unknown) stroke (*P*≥0.12 for all), ICH (*P*≥0.47 for all), or major bleeding (*P*≥0.36 for all). No NOAC in any of the subgroup analyses of patients with previous stroke or TIA of the 3 pivotal trials was shown to significantly reduce ischemic stroke versus warfarin; however, the sample size of patients with a previous history of ischemic stroke/TIA was relatively low. The more frequent use of rivaroxaban compared with other NOACs observed in our real-world analysis of previous stroke or TIA patients may suggest a preference for rivaroxaban in this population because of the high proportion of patients with previous stroke/TIA (55%) randomized in ROCKET AF (the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) compared with apixaban or dabigatran (19% and 20%, respectively) in their phase III trials.

A previous real-world analysis of dabigatran compared with vitamin K antagonist therapy among NVAF patients with previous history of stroke/TIA has been published by Larsen et al[8] and showed results not dissimilar from our own dabigatran versus warfarin analysis. Larsen et al used the Danish nationwide databases and demonstrated that vitamin K

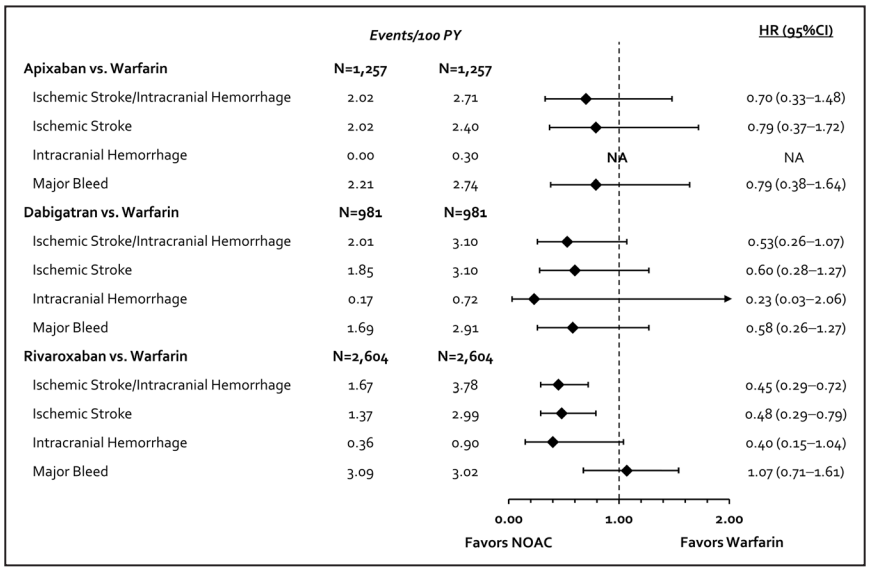

Figure 2. Event rates and hazard ratios (HRs) for each propensity score–matched non–vitamin K antagonist oral anticoagulant (NOAC) vs warfarin comparison. CI indicates confidence interval; NA, not applicable; and PY, person-years.

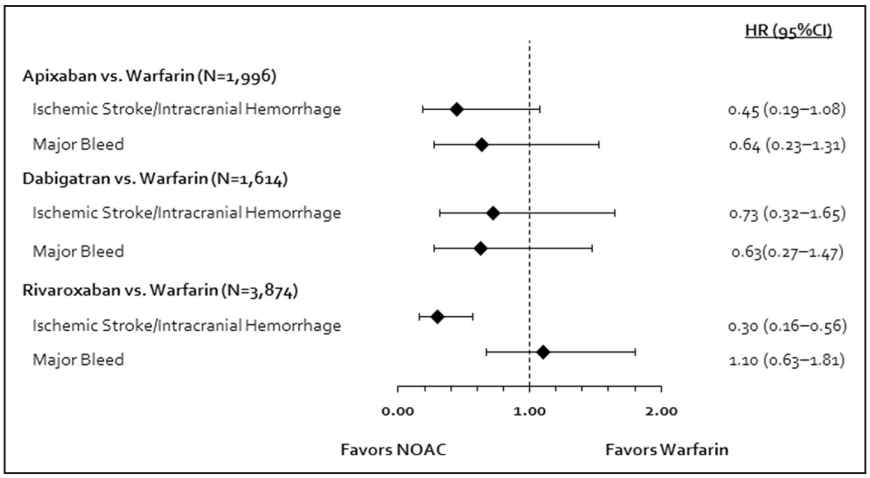

Figure 3. Hazard ratios (HRs) for each propensity score–matched standard of dose non–vitamin K antagonist oral anticoagulant (NOAC; included apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily) vs warfarin comparison. CI indicates confidence interval.

antagonist–naive patients with a history of stroke/TIA receiving either the 110 mg (n=793) or 150 mg (n=646) twice daily dose of dabigatran and 1:2 matched to vitamin K antagonist users had a lower or similar hazard of developing a recurrent stroke/TIA (dabigatran 110 mg users: HR, 0.64; 95% confidence interval, 0.50–0.80; dabigatran 150 mg users: HR, 0.92; 95% confidence interval, 0.73–1.15) during an average follow-up of 12.6 months. Of note, this study did not report data on bleeding rates among secondary stroke prevention patients.

There is a scarcity of comparative outcomes data for NOACs (either versus warfarin or a comparator NOACs) available from large prospective registries of NVAF patients. Current prospective registry studies have mainly been performed/analyzed as noninterventional, single-arm studies of NVAF all-comers and provide data on adjudicated real-world rates of outcomes, such as stroke and major bleeding.[14–17] The event rates for stroke and major bleeding seen in our study were often higher than observed in prospective registry studies of NOACs of all-comers.[14–17] This is not unexpected because previous stroke populations are at higher risk than nonprevious stroke patients for both stroke and bleeding.[1] In addition, claims database analyses often report somewhat higher event rates than prospective registry studies (potentially because of the lack of adjudication of events in claims databases).[18] Finally, the HRs seen in our secondary stroke analysis for NOAC versus warfarin are similar in magnitude with previous NOAC/NVAF claims database analyses evaluating patients both with and without a past history of stroke/TIA,[7,9,10] reinforcing the effectiveness and safety of NOACs in NVAF patients.

It is important to be aware that 3 separate, statistically independent propensity score–matched analyses of apixaban:warfarin, dabigatran:warfarin, and rivaroxaban:warfarin were conducted and are presented in this study. Because these were statistically independent analyses, we anticipate differences not only in the characteristics of NOAC users, but also among the warfarin users, as the characteristics of each warfarin cohort will be driven by the characteristic of the NOAC group they are matched to (ie, if 1 NOAC is given to a sicker population than others, we would expect the corresponding propensity score–matched warfarin cohort to also be sicker than the other warfarin cohorts). Therefore, we strongly discourage any cross-comparison between oral anticoagulation groups or analyses because this may result in inaccurate conclusions.

As a retrospective analysis of claims data, this study has limitations worthy of discussion. First, both misclassification (measurement error) and selection bias (selection of patients in a nonrandomized fashion) are always important limitations in claims database studies and may impact a study's internal and external validity, respectively.[19] Second, we used US claims data (both commercial and Medicare Advantage), and therefore, our results are most generalizable to a US population. Third, because the 110 mg twice

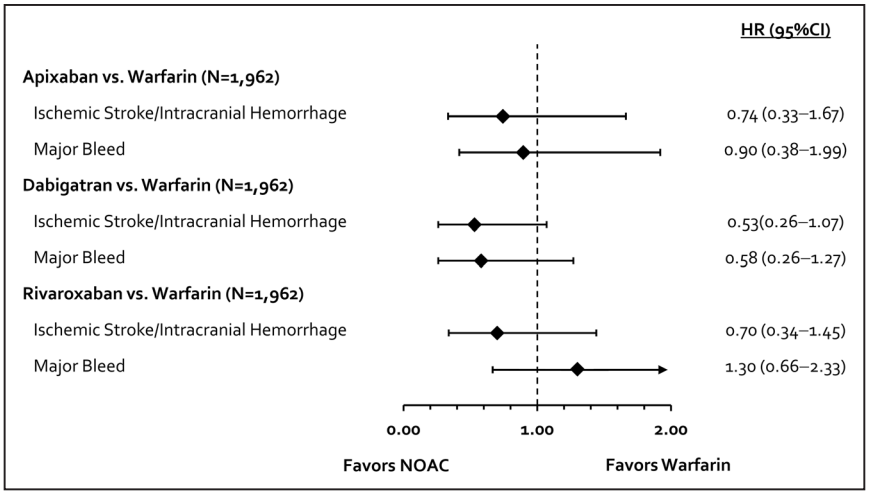

Figure 4. Hazard ratios (HRs) for each shrunken propensity score–matched non–vitamin K antagonist oral anticoagulant (NOAC) vs warfarin comparison. CI indicates confidence interval.

daily dose of dabigatran is not approved in the US (only a 75 mg twice daily dose), we were not able to determine the effectiveness or safety of the 110 mg dose which is used in other countries. Fourth, although propensity score matching[12] can generate cohorts that are comparable in key characteristics, only those variables measured in MarketScan databases could be used for matching in this analysis. Therefore, regardless of the sophistication of the methodology and the number of variables used in developing propensity scores, residual confounding cannot be excluded. Next, the majority of administrative claims databases, including MarketScan, are hampered by insufficient reporting of clinical and laboratory data.[5,19] International normalized ratio measurements were not available, and consequently, times in the therapeutic range could not be calculated. The approximate 10% poorer therapeutic range control often seen in routine US clinical practice[20] may explain some of the incremental benefits seen with the NOACs, particularly rivaroxaban, in this study compared with RCTs. Finally, the accuracy of the common on-treatment approach to claims database analysis relies on the ability to accurately determine whether patients were still taking their oral anticoagulant. We used a 14-day permissible gap in available anticoagulation based on refill records, which is common in claims database analyses. However, gaps as small as 3 days and as large as 60 days have been used.[11,21] Using too short a permissible gap may increase the likelihood of a patient being mistakenly censored in an on-treatment analysis. Conversely, too long a gap can result in patients being followed despite discontinuing oral anticoagulation treatment (and consequently at higher risk of ischemic stroke). It is also important to note that it is more difficult to accurately estimate time of drug discontinuation with warfarin compared with NOACs because of the nature of warfarin prescribing (eg, frequent dosing changes).

In conclusion, results from our study of the 3 NOACs versus warfarin in NVAF patients with a previous history of stroke/TIA are relatively consistent with their respective phase III trials and previous stroke/TIA subgroup analyses. All NOACs seemed no worse than warfarin in respect to ischemic stroke, ICH, or major bleeding risk.

Sources of Funding

This study was supported by Bayer AG, Berlin, Germany. The sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Disclosures

C.I. Coleman reports grants from Bayer AG during the conduct of the study, grants from Janssen Scientific Affairs LLC, grants from Bayer Pharma AG, grants from Pfizer, and grants from outside the submitted work. Dr Peacock reports grant funding and consultancy fees from Abbott, Alere, Banyan, Cardiorentis, Janssen Pharmaceuticals, Portola, Roche, The Medicines Company, Prevencio, and Singulex. Dr Alberts reports consultancy fees and honoraria from and is on the speakers bureau of Genentech, Janssen Pharmaceuticals, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Medscape; consultancy fees and honoraria from Nestle, Daiichi Sankyo, and Portola; honoraria from and is on the speakers bureau of Chiesi USA, Inc; and patents/royalties from Duke University. The other author reports no conflict.

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