CURRENT MEDICAL RESEARCH AND OPINION, 2016
http://dx.doi.org/10.1080/03007995.2016.1237937
Article FT-0400.R2/1237937

Taylor & Francis
Taylor & Francis Group

BRIEF REPORT

Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study

Craig I. Coleman[a], Matthias Antz[b], Kevin Bowrin[c], Thomas Evers[d], Edgar P. Simard[e], Hendrik Bonnemeier[f] and Riccardo Cappato[g]

[a]University of Connecticut School of Pharmacy, Storrs, CT, USA; [b]Hospital Oldenburg, Department of Cardiology, Oldenburg, Germany; [c]Bayer Pharma AG, Berlin, Germany; [d]Bayer Pharma AG, Wuppertal, Germany; [e]Aetion Inc., New York, NY, USA; [f]University Medical Center of Schleswig-Holstein, Department of Electrophysiology and Rhythmology, Kiel, Germany; [g]Arrhythmia and Electrophysiology Research Center, Humanitas Clinical and Research Center, Rozzano, MI, Italy

ABSTRACT

Background: Little data exists regarding the effectiveness and safety of rivaroxaban or apixaban versus warfarin in nonvalvular atrial fibrillation (NVAF) patients treated outside of clinical trials.

Methods: This was a retrospective study using MarketScan claims from January 2012 to October 2014. We included adults, newly initiated on rivaroxaban, apixaban or warfarin, with a baseline CHA_2DS_2-VASc score ≥ 2, ≥ 2 diagnosis codes for NVAF and ≥ 180 days of continuous medical and prescription benefits. Patients with a prior stroke, systemic embolism or intracranial hemorrhage (ICH) were excluded. Eligible rivaroxaban or apixaban users were 1:1 propensity-score matched individually to warfarin users. Cox regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for rivaroxaban and apixaban versus warfarin for the combined endpoint of ischemic stroke or ICH and each endpoint individually.

Results: Upon matching 11,411 rivaroxaban to 11,411 warfarin users, rivaroxaban was associated with a significant reduction of the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.61, 95% CI = 0.45–0.82). ICH was significantly (HR = 0.53, 95% CI = 0.35–0.79) and ischemic stroke nonsignificantly reduced (HR = 0.71, 95% CI = 0.47–1.07) by rivaroxaban versus warfarin. After matching 4083 apixaban and 4083 warfarin users, apixaban was found to nonsignificantly reduce the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.63, 95% CI = 0.35–1.12) and to reduce ICH risk (HR = 0.38, 95% CI = 0.17–0.88). Ischemic stroke risk was nonsignificantly increased with apixaban (HR = 1.13, 95% CI = 0.49–2.63) versus warfarin.

Limitations: Sample size and number of combined events observed were relatively small. Residual confounding could not be ruled out.

Conclusions: Rivaroxaban and apixaban were associated with less ICH than warfarin and both are likely associated with reductions in the combined endpoint. Further investigation to validate the numerically higher rate of ischemic stroke with apixaban versus warfarin is required.

ARTICLE HISTORY
Received 10 August 2016
Revised 13 September 2016
Accepted 13 September 2016
Published online 20 September 2016

KEYWORDS
Anticoagulants; Apixaban; Nonvalvular atrial fibrillation; Rivaroxaban; Stroke prevention; Warfarin

Introduction

Nonvalvular atrial fibrillation (NVAF) is a common cardiac arrhythmia affecting up to 6.1 million persons in the US, and is associated with a ~5-fold increased risk of stroke[1]. Current NVAF guidelines recommend initiation of oral anticoagulant (OAC) therapy based on validated stroke risk scores.

Randomized controlled trials (RCTs)[2–4] have demonstrated favorable efficacy and safety profiles for the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) compared to warfarin. Most notably, these direct-acting OACs have been shown to significantly reduce patients' risk for intracranial hemorrhage (ICH) by 33–58%.

In routine clinical practice, OACs may be used differently than in their respective pivotal, phase III RCTs. When rigorously performed, real-world evidence studies (including administrative claims database analyses) can offer valuable insight into the effectiveness and safety of OACs used outside of a well controlled clinical trial setting. The objective of the Real-world EVIdence on Stroke prevention In patients with aTrial fibrillation in the United States (REVISIT-US) study was to affirm the effectiveness and safety of previously OAC treatment naïve, newly initiated factor Xa inhibition with rivaroxaban or apixaban compared with warfarin in NVAF patients using data from a large, US administrative claims database.

Patients and methods

This manuscript was written in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[5].

CONTACT Craig I. Coleman PharmD, Professor craig.coleman@hhchealth.org University of Connecticut, School of Pharmacy, 69 North Eagleville Road, Storrs, CT 06269-3092, USA

REVISIT-US was a retrospective administrative claims database study using US Truven MarketScan data spanning January 2012 through October 2014. MarketScan combines two 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 US[6]. MarketScan captures health plan enrollment records, limited participant demographics, International Classification of Diseases, Ninth-Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, admission and discharge dates, inpatient mortality data and outpatient medical services and prescription drug dispensing records. All data included in the MarketScan database are de-identified 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 REVISIT-US, patients had to be OAC treatment naïve in the 180 days prior to the day of the first qualifying OAC dispensing, newly initiated on rivaroxaban, apixaban, or warfarin, ≥18 years of age on the day of the first qualifying OAC dispensing (index date), with a baseline CHA_2DS_2-VASc score ≥2[1], ≥2 ICD-9-CM diagnosis codes for NVAF (427.31) and ≥180 days of continuous medical and prescription coverage prior to initiation of OAC. Patients with valvular heart disease, a transient cause of NVAF, venous thromboembolism, hip or knee replacement surgery, malignant cancer or pregnancy, and patients receiving OAC before the index date, or prescribed >1 OAC agent on the index date or during follow-up were excluded. In addition, we excluded patients with a prior history of stroke, systemic embolism or ICH from the analysis to prevent misclassification of past events as new events.

Each eligible rivaroxaban user was 1:1 propensity-score matched (using greedy nearest neighbor matching and a caliper of 1%) to a warfarin user to minimize the presence of baseline differences between cohorts[7]. Similarly, each eligible apixaban user was 1:1 propensity-score matched to a warfarin user. As a result of the above described matching process, this study reports on two unique analyses (rivaroxaban versus warfarin and apixaban versus warfarin) with different sample sizes. We included rivaroxaban and apixaban patients starting at each agent's individual US Food and Drug Administration (FDA) approval date (November 2011 for rivaroxaban and December 2012 for apixaban)[8] and only matched these patients to warfarin users initiating OAC during the same time frame. Residual differences in characteristics between matched cohorts were assessed by calculating the standardized differences, with differences <10% between cohorts considered balanced[9]. Patients were matched using age, gender, region, health plan type, $CHADS_2$, CHA_2DS_2-VASc, ATRIA, modified HAS-BLED (excluding the liable international normalized ratio criteria) and Deyo–Charlson Comorbidity Index scores[1,10–12], presence of comorbid heart failure, hypertension, diabetes mellitus, unstable angina or renal failure, use of anti-arrhythmic agents, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, anti-platelet agents or nonsteroidal anti-inflammatory drugs and number of hospital days and office visits during the 180 day index period.

The primary endpoint evaluated in REVISIT-US was the combination of ischemic stroke or ICH (reflecting the most important efficacy and safety endpoints with comparable severity in OAC trials). Each component of this endpoint was also evaluated separately. Occurrence of these endpoints during the observation period was determined by the presence of an ICD-9-CM code as recommended by US FDA "Mini-Sentinel" post-marketing surveillance system[13] coding schemas. Patients were followed until the occurrence of an ischemic stroke or ICH, discontinuation or switching to an alternative OAC, disenrollment from the insurance plan or end of study follow-up.

Baseline characteristics of patients were analyzed using descriptive statistics. Incidence rates of endpoints were reported as the number of events per 100 person-years (or %/year). Cox proportional hazard regression analysis was performed to estimate the hazard ratio (HR) with 95% confidence intervals (CIs) for developing each endpoint. Analyses were performed in Aetion Evidence Generation Platform – Effectiveness Evaluation Application version R2.0.20160113_2214-0-g6871884 (Aetion Inc., New York, NY, USA). Statistical testing was done in Aetion using R version 3.1.2 (The R Project for Statistical Computing, www.r-project.org)[14]. In all cases, a *P*-value <.05 was considered statistically significant.

Results

In total, 38,831 NVAF patients newly initiated on rivaroxaban or warfarin meeting inclusion criteria were identified (Figure 1). Of these, 10.5% of rivaroxaban patients and could not be adequately matched and were therefore excluded from the analyses. Following propensity scoring, 11,411 rivaroxaban (17.3% received the reduced 15 mg once daily) and 11,411 warfarin users were matched. Characteristics and person-years of follow-up of these rivaroxaban and warfarin cohorts are available in Table 1. The two cohorts were well matched, with no characteristic exhibiting a standardized difference >10%. Seventy-three rivaroxaban and 103 warfarin users developed the combined endpoint, translating into a significant 39% (95% CI = 18–55%) lower hazard of developing ischemic stroke or ICH among rivaroxaban users (Figure 2). When analyzed separately, the hazard of both ICH and ischemic stroke were reduced with rivaroxaban use (47% and 29% lower) compared to warfarin, although reduction of the ischemic stroke endpoint did not reach statistical significance (42 versus 52 ischemic strokes and 38 versus 60 ICHs in rivaroxaban and warfarin users, respectively).

We identified 18,591 apixaban (15.5% received the reduced dose) or warfarin patients meeting inclusion criteria. Of these, 5.7% of apixaban patients could not be adequately matched and were therefore excluded from the analyses. Upon propensity scoring and matching, well matched (no standardized differences >10%) cohorts consisting of 4083 apixaban and 4083 warfarin users were included (Table 2). Nineteen apixaban and 28 warfarin users experienced the

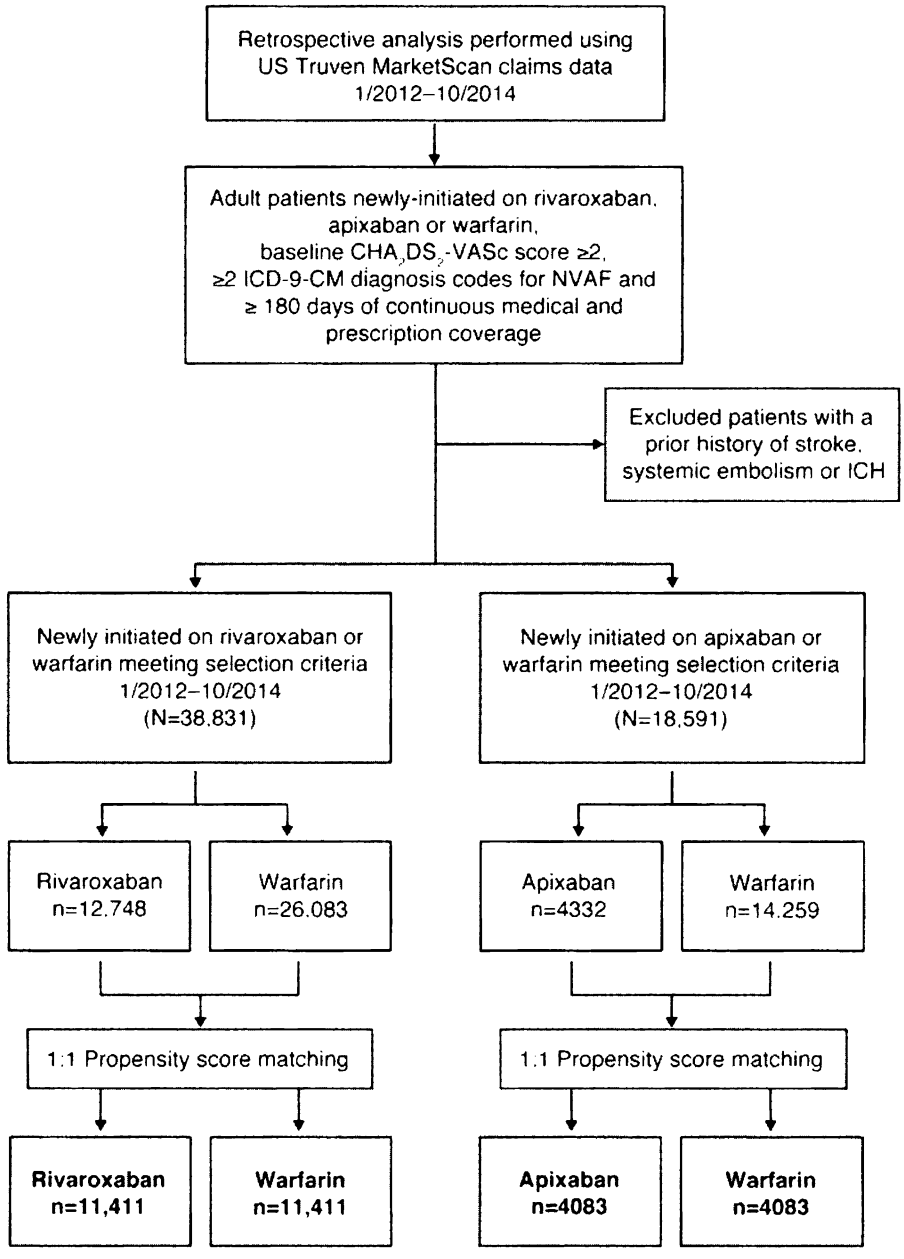

Figure 1. Patient flow diagram for the rivaroxaban versus warfarin and apixaban versus warfarin analyses. Abbreviations. ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICH, intracranial hemorrhage; NVAF, nonvalvular atrial fibrillation.

combined endpoint of ischemic stroke or ICH (hazard reduction with apixaban = 37%, P = NS) (Figure 3). This finding was driven by a significant 62% reduction in ICH with apixaban (8 versus 19 events) and a 13% statistically nonsignificant increase in ischemic stroke hazard with apixaban (12 versus 10 events) compared to warfarin.

Discussion

This administrative claims database study affirmed that both rivaroxaban and apixaban use were associated with significant (47–62%) reductions in NVAF patients' hazard of developing ICH compared to warfarin in routine clinical practice. 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) trial[2], rivaroxaban was found to reduce the risk of ICH by 33% and in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[3], apixaban reduced ICH by 58% versus warfarin ($P < .05$ for both). We believe our findings regarding ICH reduction should be reassuring to clinicians as they are generally consistent with those of the above-mentioned pivotal phase III trials. Notably, the reductions in ICH seen in REVISIT-US were the predominant drivers of the reductions in the combined endpoint observed with both rivaroxaban and apixaban versus warfarin (albeit only the rivaroxaban analysis reached statistical significance).

We found rivaroxaban to be associated with a nonsignificant reduced hazard of ischemic stroke versus warfarin in the present study. Apixaban was associated with a nonsignificant

Table 1. Baseline characteristics of propensity-score matched rivaroxaban and warfarin users.

Characteristic	Rivaroxaban ($N = 11,411$) n (%) (7715 PYs)	Warfarin ($N = 11,411$) n (%) (6271 PYs)	Standardized difference, %
Cohort entry (year)			0.9
2012	3132 (27.4)	3080 (27.0)	
2013	4764 (41.7)	4810 (42.2)	
2014	3515 (30.8)	3521 (30.9)	
Age, years (mean ± SD)	70.66 ± 10.99	70.72 ± 11.35	0.6
Male gender	6115 (53.6)	6145 (53.9)	
US region			0.5
Northeast	2342 (20.5)	2358 (20.7)	
North Central	3220 (28.2)	3212 (28.1)	
South	3936 (34.5)	3917 (34.3)	
West	1734 (15.2)	1745 (15.3)	
Unknown	179 (1.6)	179 (1.6)	
Health plan			1.3
Basic/major medical	0 (0)	0 (0)	
Comprehensive	3523 (30.9)	3516 (30.8)	
EPO	47 (.4)	51 (.4)	
HMO	1101 (9.6)	1117 (9.8)	
POS	544 (4.8)	533 (4.7)	
PPO	5517 (48.3)	5500 (48.2)	
POS with capitation	55 (.5)	53 (.5)	
CDHP	248 (2.2)	260 (2.3)	
HDHP	134 (1.2)	134 (1.2)	
Missing	242 (2.1)	247 (2.2)	
Stroke risk scores			
$CHADS_2$ (mean ± SD)	1.92 ± 1.08	1.94 ± 1.08	1.7
CHA_2DS_2-VASc (mean ± SD)	3.46 ± 1.37	3.48 ± 1.35	1.8
Bleeding risk scores			
ATRIA score (mean ± SD)	1.76 ± 1.51	1.76 ± 1.55	0.4
HAS-BLED score (mean ± SD)	1.62 ± .69	1.62 ± .71	0.9
Comorbidities			
Deyo–Charlson Comorbidity Score (mean ± SD)	1.08 ± 1.10	1.09 ± 1.10	1.1
Heart failure	2259 (19.8)	2282 (20.0)	0.5
Hypertension	10,658 (93.4)	10,691 (93.7)	1.2
Diabetes mellitus	3913 (34.3)	3980 (34.9)	1.2
Renal failure	135 (1.2)	136 (1.2)	0.1
Medications			
Antiarrhythmics	1890 (16.6)	1912 (16.8)	0.5
Beta-blockers	5832 (51.1)	5866 (51.4)	0.6
Calcium channel blockers	3926 (34.4)	3953 (34.6)	0.5
Angiotensin-converting enzyme inhibitors	433 (3.8)	442 (3.9)	0.4
Angiotensin receptor blockers	2239 (19.6)	2297 (20.1)	1.3
Antiplatelet medications	1259 (11.0)	1239 (10.9)	0.6
Nonsteroidal anti-inflammatory drugs	1858 (16.3)	1823 (16.0)	0.8
Healthcare utilization (180 days prior to index date)			
Days in hospital (mean ± SD)	2.00 ± 4.37	2.02 ± 4.82	0.6
Number of office visits (mean ± SD)	7.37 ± 7.58	7.33 ± 7.68	0.4

Abbreviations. CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; PPO, preferred provider organization; POS, point-of-service; PY, person-year; SD, standard deviation.

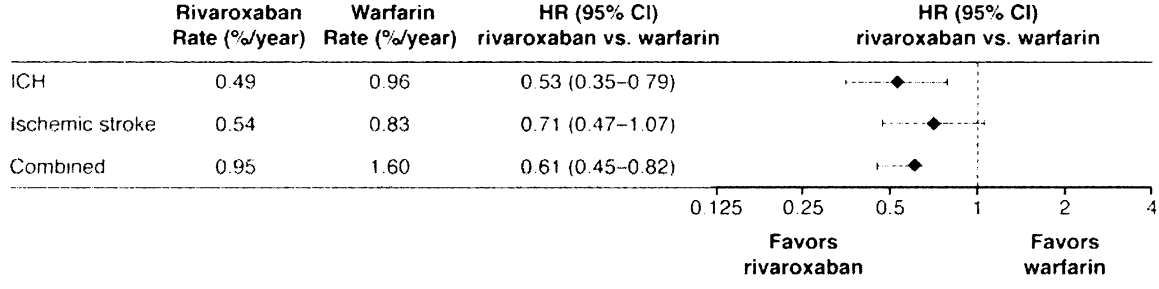

Figure 2. Impact of rivaroxaban versus warfarin on study endpoints. Abbreviations. CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage.

13% increased hazard of ischemic stroke. The reduction in ischemic stroke with rivaroxaban is generally consistent with ROCKET AF (HR = 0.94, 95% CI = 0.75–1.17)[2]. The 13% increased hazard of ischemic stroke observed in apixaban users compared to warfarin users is less consistent with ARISTOTLE (HR = 0.92, 95% CI = 0.74–1.13)[3]. This finding of a numerically higher ischemic stroke risk with apixaban in routine practice is supported by prior studies[15,16].

Table 2. Baseline characteristics of propensity-score matched apixaban and warfarin users.

Characteristic	Apixaban ($N = 4083$) *n* (%) (2125 PYs)	Warfarin ($N = 4083$) *n* (%) (1951 PYs)	Standardized difference
Cohort entry (year)			0.5
2012	0 (0)	0 (0)	
2013	1502 (36.8)	1493 (36.6)	
2014	2581 (63.2)	2590 (63.4)	
Age, years (mean ± SD)	71.00 ± 11.25	71.15 ± 11.32	1.3
Male gender	2172 (53.2)	2189 (53.6)	0.8
US region			2.4
Northeast	832 (20.4)	851 (20.8)	
North Central	1142 (28.0)	1158 (28.4)	
South	1496 (36.6)	1475 (36.1)	
West	538 (13.2)	532 (13.0)	
Unknown	75 (1.8)	67 (1.6)	
Health plan			4.2
Basic/major medical	0 (0)	0 (0)	
Comprehensive	1252 (30.7)	1260 (30.9)	
EPO	12 (.3)	6 (.1)	
HMP	361 (8.8)	347 (8.5)	
POS	190 (4.7)	205 (5.0)	
PPO	1996 (48.9)	2000 (49.0)	
POS with capitation	16 (.4)	14 (.3)	
CDHP	137 (3.4)	128 (3.1)	
HDHP	65 (1.6)	67 (1.6)	
Missing	54 (1.3)	56 (1.4)	
Stroke risk scores			
$CHADS_2$ score (mean ± SD)	1.93 ± 1.07	1.92 ± 1.07	0.9
CHA_2DS_2-VASc score (mean ± SD)	3.47 ± 1.38	3.47 ± 1.35	0.5
Bleeding risk scores			
ATRIA score (mean ± SD)	1.84 (1.59)	1.86 (1.66)	1.1%
HASBLED score (mean ± SD)	1.65 (.69)	1.66 (.72)	1.3%
Comorbidities			
Deyo–Charlson Comorbidity Score (mean ± SD)	1.05 ± 1.08	1.03 ± 1.08	1.7
Heart failure	778 (19.1)	776 (19.0)	0.1
Hypertension	3876 (94.9)	3863 (94.6)	1.4
Diabetes mellitus	1392 (34.1)	1381 (33.8)	0.6
Renal failure	72 (1.8)	73 (1.8)	0.2
Medications			
Antiarrythmics	851 (20.8)	858 (21.0)	0.4
Beta-blockers	2285 (56.0)	2258 (55.3)	1.3
Calcium channel blockers	1514 (37.1)	1461 (35.8)	2.7
Angiotensin-converting enzyme inhibitors	157 (3.8)	152 (3.7)	0.6
Angiotensin receptor blockers	817 (20.0)	843 (20.6)	1.6
Antiplatelet medications	443 (10.8)	443 (10.8)	0
Nonsteroidal anti-inflammatory drugs	681 (16.7)	680 (16.7)	0.1
Healthcare utilization (180 days prior to index date)			
Hospital days (mean ± SD)	1.81 ± 4.22	1.81 ± 4.10	0
Office visits (mean ± SD)	7.54 ± 7.30	7.28 ± 7.60	3.5

Abbreviations. CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; PPO, preferred provider organization; POS, point-of-service; PY, person-year; SD, standard deviation.

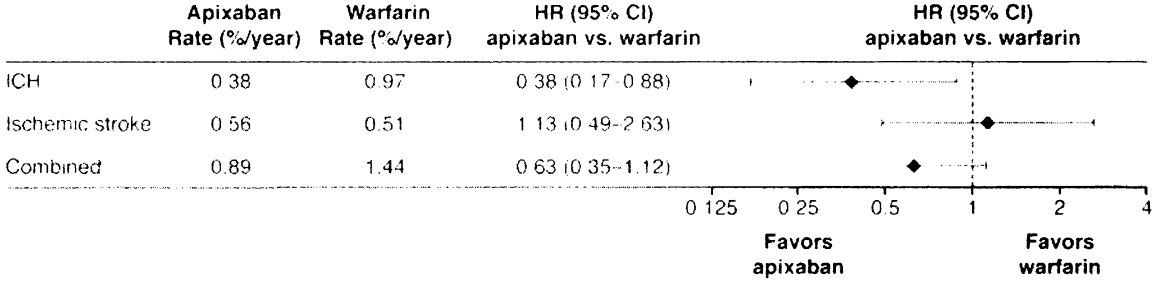

Figure 3. Impact of apixaban versus warfarin on study endpoints. Abbreviations. CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage.

In an independent analysis, Noseworthy and colleagues[15] found apixaban to be associated with a 27% (1.04 versus 0.73 events per 100 person-years, $P = .39$) increased hazard of ischemic stroke compared to rivaroxaban in an Optum Labs Data Warehouse claims study utilizing data from October 2010 to February 2015 (median age = 73 years; CHA_2DS_2-VASc score = 4 in both matched cohorts). Thus, one potential explanation for the numerical increase in ischemic stroke for apixaban versus warfarin seen in our analysis could be the more frequent use of the reduced 2.5 mg twice daily dose in routine clinical practice (15.5% received the reduced apixaban dose in REVISIT-US versus 4.6% in ARISTOTLE)[3].

For rivaroxaban the use of the reduced dose was more consistent with ROCKET AF (17.3% received the reduced 15 mg once daily rivaroxaban dose in REVISIT-US versus 20.7% in ROCKET AF)[2,17].

In addition, poor adherence to the twice daily dosing regimen of apixaban outside of controlled trials may also have contributed to our findings[18–22]. Studies suggest that suboptimal adherence (taking <80% of one's doses) among NVAF patients may be associated with a 50% increased risk of ischemic stroke (95% CI = 23–83%)[18]. Moreover, Shore and colleagues[22] found that every 10% reduction in dabigatran adherence was associated with a 13% (95% CI = 8–19%) increased hazard of all-cause mortality or stroke. Available data from real-world evidence suggests that the use of apixaban in routine practice may be associated with more ischemic strokes versus warfarin, and this finding merits further investigation.

REVISIT-US was specifically designed to the extent possible within a claims database to optimize internal study rigor and, therefore, obtain the most unbiased HR estimates for rivaroxaban and apixaban compared to warfarin. In order to achieve our goal, we selected endpoints that were most likely to be accurately identified through ICD-9-CM coding in MarketScan and that were associated with similar degrees of morbidity and mortality to assist readers in drawing benefit–risk conclusions. Moreover, we used validated ICD-9-CM coding schemas[14] and excluded patients with prior stroke, systemic embolism or ICH (which may have contributed to the low number of events)[23]. Each of these methodological steps was taken to attenuate the risk of potential misclassification bias common to claims database analyses. Finally, because rivaroxaban and apixaban were approved at different times, and clinician experience and comfort with prescribing these agents likely grows over time potentially changing benefit and risk assessment, rivaroxaban and apixaban users were included starting at their respective US FDA approval dates and only matched to warfarin users initiating anticoagulation during the same time frame.

We feel it is also important for readers to be cognizant that two separate analyses (rivaroxaban versus warfarin and apixaban versus warfarin) were performed and presented in this paper. As these were statistically independent analyses, we discourage cross-comparison between the rivaroxaban and apixaban cohorts or between the two corresponding warfarin cohorts as this may not yield robust conclusions. The primary objective of our analyses was to show consistency between real-world claims database analysis and phase III RCTs, and not to draw comparisons between OACs that have not been rigorously compared in head-to-head RCTs. Direct comparison of rivaroxaban and apixaban in MarketScan is hampered by the database's insufficient reporting of laboratory (serum creatinine) and clinical data (body weight) which are required to determine whether rivaroxaban and apixaban prescribing was consistent with labeling.

This study has additional limitations worthy of discussion. First, while propensity-score matching generated cohorts that were comparable in key characteristics, only those variables measured in MarketScan could be matched upon and residual confounding cannot be excluded. Second, MarketScan has a substantial lag in time to data availability. As a result, upon securing this data and performing analysis in early 2016, MarketScan data was only available through October 2014. This meant there were only about 4000 eligible apixaban users in this dataset. Given that RCTs of rivaroxaban[2] and apixaban[3] have enrolled >7000 subject per study arm, it is likely that the apixaban analyses were somewhat underpowered and any apixaban versus rivaroxaban comparison would be more so. With this in mind, it is important to remember that failure to show a significant difference between agents, in studies such as the one presented, is not proof of equivalence or noninferiority. Finally, it was not possible to determine the duration of time warfarin users spent in the therapeutic international normalized ratio (INR) range of 2.0–3.0. Additional analyses evaluating the effectiveness and safety of the direct-acting OACs should be performed once sample sizes in claims databases grow larger.

Conclusion

In this real-world analysis of NVAF patients within the United States, both rivaroxaban and apixaban use was associated with less ICH than warfarin. This data confirms results of these agents' corresponding phase III clinical trials. Both rivaroxaban and apixaban appear likely associated with reductions in the combined endpoint of ICH or ischemic stroke versus warfarin as well. While only a preliminary finding based upon a relatively small number of events, further investigation into the numerically (but not statistically) higher rate of ischemic stroke with apixaban versus warfarin is required.

Transparency

Declaration of funding

The REVISIT-US study was supported by Bayer Pharma AG.

Declaration of financial/other relationships

C.I.C. has disclosed that he has received grant funding and consultancy fees from Janssen Pharmaceuticals, Bayer and Boehringer Ingelheim Pharmaceuticals. M.A. has disclosed that he has received consulting fees and speaker honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daichii Sankyo and Pfizer. E.P.S. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article. T.E. and K.B. have disclosed that they are employees of Bayer Pharma AG. H.B. has disclosed that he has received honoraria for lectures from Advanced Circulatory Systems, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiome, Daiichi Sankyo, Impulse-Dynamics, Jolife, NayaMed, Medtronic, Lilly, MSD, Physiocontrol, Pfizer, Sanofi, Servier, Sorin and St. Jude Medical; honoraria for advisory board activities from Bayer, Boehringer Ingelheim, Biotronik, Biosense-Webster, Bristol-Myers Squibb, Boston

Scientific, Daiichi Sankyo, Medtronic, MSD, NayaMed, Physiocontrol, Pfizer and Sanofi; been involved with clinical trials for Biotronik, CVRx, Daiichi Sankyo, Impulse Dynamics, NayaMed, Novartis, Medtronic, MSD, Respicardia, Resmed, Sorin, St. Jude Medical and Sanofi. R.C. has disclosed that he has acted as a consultant to Abbott, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, ELA Sorin, Medtronic, Pfizer and St. Jude; participated in speakers' bureaus for Abbot, BARD, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Medtronic, Sanofi and St. Jude; acted as a study investigator for Abbott, BARD, Bayer, Biosense Webster, Cameron Health, Medtronic, Pfizer and Sanofi; received grants from BARD, Biosense Webster, Boston Scientific, ELA Sorin, Medtronic, St. Jude; and holds equity and intellectual property rights in Cameron Health.

CMRO peer reviewers on this manuscript have received an honorarium from *CMRO* for their review work, but have no other relevant financial relationships to disclose.

References

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRE guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130:2071-204
2. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91
3. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92
4. Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104
5. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9
6. Truven Health Analytics. MarketScan research databases. Available at: http://truvenhealth.com/Portals/0/assets/ACRS_11223_0912_MarketScanResearch_SS_Web.pdf [Last accessed 1 May 2016]
7. D'Agostino Jr RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81
8. United States Food and Drug Administration. Drugs@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/[Last accessed 1 May 2016]
9. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009;38:1228-34
10. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58:395-401
11. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100
12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-19
13. Go AS, Singer D, Cheetham C, et al. Mini-Sentinel Medical product assessment – a protocol for assessment of dabigatran, Version 3. Available at: http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Protocol-for-Assessment-of-Dabigatran.pdf [Last accessed 15 March 2016]
14. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2013. Available at: http://www.R-project.org/[Last accessed 15 March 2016]
15. Noseworthy P, Yao X, Sangaralingham LR, et al. Direct comparison of dabigatran, rivaroxaban and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. Oral presentation in Highlighted Original Research: Arrhythmias and Clinical EP and the Year in Review at the 65th Annual Meeting of the American College of Cardiology, Chicago, IL, USA, 2016
16. Yao X, Shah ND, Sangaralingham LR, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulations in patients without severe renal impairment. Oral presentation at the 21st Annual International Meeting of the International Society of Pharmacoeconomics and Outcomes Research, Washington, DC, USA, May 2016
17. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32:2387-94
18. Alberts MJ, Peacock WF, Fields LE, et al. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. Int J Cardiol 2016;215:11-13
19. McHorney CA, Crivera C, Laliberté F, et al. Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure. Curr Med Res Opin 2015;31:2167-73
20. Coleman CI, Roberts MS, Sobieraj DM, et al. Effect of dosing frequency on chronic cardiovascular disease medication adherence. Curr Med Res Opin 2012;28:669-80
21. Coleman CI, Tangirala M, Evers T. Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with nonvalvular atrial fibrillation in the United States. Int J Cardiol 2016;212:171-3
22. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J 2014;167:810-17
23. Coleman CI, Antz M, Ehlken B, et al. REal-LIfe Evidence of stroke prevention in patients with atrial Fibrillation – the RELIEF study. Int J Cardiol 2016;203:882-4

Notice of correction

Please note that the abstract has been corrected since the article was first published online (20 September 2016)