A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system

Todd C. Villines[1]; Janet Schnee[2]; Kathy Fraeman[3]; Kimberly Siu[2]; Matthew W. Reynolds[3]; Jenna Collins[3]; Eric Schwartzman[4]

[1]Cardiology Service, Walter Reed National Military Medical Center, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA; [2]Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conneticut, USA; [3]Evidera, Lexington, Massachusetts, USA; [4]Heart and Vascular Center, Naval Medical Center, Portsmouth, Virginia, USA

Summary

Dabigatran is approved for stroke risk reduction in patients with non-valvular atrial fibrillation (NVAF). Data from diverse clinical practice settings will help establish whether the risk:benefit ratio seen in clinical trials is comparable with routine clinical care. This study aimed to compare the safety and effectiveness of dabigatran and warfarin in clinical practice. We undertook a propensity score-matched (PSM) cohort study (N=12,793 per group; mean age 74) comparing treatment with dabigatran or warfarin in the US Department of Defense claims database, October 2009 to July 2013. Treatment-naïve patients with first prescription claim for dabigatran (either FDA-approved dose) or warfarin between October 2010 and July 2012 (index) and a diagnosis of NVAF during the 12 months before index date were included. Primary outcomes were stroke and major bleeding. Secondary outcomes included ischaemic and haemorrhagic stroke, major gastrointestinal (GI), urogenital or other bleeding, myocardial infarction (MI) and death. Time-to-event was investigated using Kaplan-Meier survival analyses. Outcomes comparisons were made utilising Cox-proportional hazards models of PSM groups. Dabigatran users experienced fewer strokes (adjusted hazard ratio [95 % confidence intervals] 0.73 [0.55–0.97]), major intracranial (0.49 [0.30–0.79]), urogenital (0.36 [0.18–0.74]) and other (0.38 [0.22–0.66]) bleeding, MI (0.65 [0.45–0.95]) and deaths (0.64 [0.55–0.74]) than the warfarin group. Major bleeding (0.87 [0.74–1.03]) and major GI bleeding (1.13 [0.94–1.37]) was similar between groups and major lower GI bleeding events were more frequent (1.30 [1.04–1.62]) with dabigatran. In conclusion, compared with warfarin, dabigatran treatment was associated with a lower risk of stroke and most outcomes measured, but increased incidence of major lower GI bleeding.

Keywords

Atrial fibrillation, anticoagulant, stroke, stroke prevention, bleeding

Correspondence to:
Todd C. Villines, MD, FACC, FAHA, FACP
Director, Cardiovascular Research
Walter Reed National Military Medical Center
8901 Wisconsin Avenue, Rockville, MD 20889, USA
Tel.: +1 301 295 7839, Fax: +1 301 295 6616
E-mail todd.c.villines.mil@mail.mil

Financial support:
Boehringer Ingelheim Pharmaceuticals, Inc funded this research.

Received: June 5, 2015
Accepted after major revision: September 28, 2015
Epub ahead of print: October 8, 2015

http://dx.doi.org/10.1160/TH15-06-0453
Thromb Haemost 2015; 114: 1290–1298

Introduction

Atrial fibrillation (AF) is estimated to affect more than 5 million people in the United States, with prevalence predicted to rise to 12 million by 2030 (1). With a lifetime risk of developing AF of approximately 25 %, AF is the most common cardiac rhythm disorder seen in clinical practice (2, 3).

Vitamin K antagonists, such as warfarin, have been shown to reduce risk of stroke and death in patients with AF (4, 5). While anticoagulation also increases risk of bleeding, for many patients the risk:benefit ratio of treatment is favourable, and recent American Heart Association/American College of Cardiology/Heart Rhythm Society atrial fibrillation treatment guidelines support that antithrombotic therapy for all patients be based on shared decision making, discussion of risks of stroke and bleeding, and patient preferences (6). Until recently, warfarin was the only oral anticoagulant available in the United States. It is highly effective when well managed but has multiple interactions with food and drugs, and requires frequent laboratory monitoring and dose adjustment as needed to ensure its therapeutic range is maintained.

In recent years, multiple non-vitamin K dependent oral anticoagulants (NOACs), which do not require frequent laboratory monitoring and dose adjustments, have been approved on the basis of large, randomised controlled trials (7). Dabigatran, a direct thrombin inhibitor (8), was the first such agent approved by the US Food and Drug Administration (FDA) in 2010 for stroke and systemic embolism risk reduction in nonvalvular AF (NVAF) patients on the basis of the Randomized Evaluation of Long-Term Anticoagulation therapy (RE-LY) trial (9, 10). This study included over 18,000 patients randomised to one of two doses of dabigatran (110 mg or 150 mg bid) or to warfarin managed for a target international normalised ratio (INR) of 2.0 to 3.0. The study was blinded for dabigatran dose (110 mg vs 150 mg) but open for dabigatran versus warfarin. In RE-LY, dabigatran 110 mg was associated with similar rates of stroke and systemic embolism as warfarin but lower rates of major haemorrhage, whereas dabigatran 150 mg was associated with lower rates

of stroke and systemic embolism as warfarin but similar rates of major haemorrhage. Of note, the US FDA approved the 150-mg dose but not the 110-mg dose for patients with creatinine clearance (CrCl) > 30 ml/minute (min), as in RE-LY, but additionally approved 75 mg bid (a dose not included in RE-LY) for patients with CrCl 15–30 ml/min, based on PK modelling, which supported that this dose would achieve exposures similar to those achieved in the RE-LY 150-mg dose group.

While safety and efficacy of dabigatran compared with well-controlled warfarin have been demonstrated in the clinical trial setting, there may be important differences in the selection, treatment, and management of patients in clinical practice versus those in clinical trials. Therefore, careful evaluation of the safety and effectiveness of this agent across multiple clinical practice settings is also important. The Department of Defense (DoD) operates one of the largest health care databases in the United States. This fully budgeted $55 billion health care system provides uniform medical coverage and pharmacy benefits for approximately 10 million people. Covered participants who fill prescriptions at military and non-military pharmacies or via home delivery have no (if filled at a military pharmacy) or a modest co-payment for medications, and their benefits are not capped. The Medicare Part D prescription drug benefit, by comparison, includes a beneficiary-paid deductible before benefits begin, 25% co-payments, and the so-called "donut hole" coverage gap between the initial coverage limit and the patient's maximum annual cost. The DoD database has previously been used to compare treatment persistence with dabigatran and warfarin in treatment-naïve patients newly diagnosed with NVAF (11). Here, we use it to compare the safety and effectiveness of dabigatran and warfarin in more than 25,000 patients diagnosed with NVAF in clinical practice.

Methods

Study design

This was a cohort analysis of existing data from the DoD database. The timings of the study are defined below:

- The **index date** was first prescription claim for dabigatran (either FDA-approved dose) or warfarin between October 1, 2010 and July 31, 2012.
- The overall **study period** was from October 1, 2009 to July 31, 2013.
- The **baseline period** was the 12 months prior to and including the index date (minimum duration in the database was, thus, 1 year).
- The **follow-up period** began on the day after the index date and ended on the earliest of the following: the day of treatment discontinuation, the day before a switch to a different anticoagulant, the end of continuous eligibility of a patient in the health plan (disenrollment), the end of the study period, or death of the patient.

Exposure to the index drug was considered discontinued if there was a treatment gap longer than 30 days past the end of the continuous treatment episode, derived from the number of days of supply of the last prescription. Once patients experienced a specific outcome event, they were censored for further consideration of that event but continued to be followed for other events.

Sensitivity analyses were conducted using 45 and 60 allowable gap days to define duration of exposure to drug. For warfarin patients, additional sensitivity analyses were performed using allowable gaps between treatments of 45 and 60 days but also allowing treatment gaps to be extended by looking at INR measurements during these gaps as proxy indicators of drug use (Go et al. method [12]). For gaps longer than 30 days, patients were considered to be continually taking warfarin if there were intervening INR tests at least every 42 days extending into the next post-gap warfarin interval. This grace period of 30 days at the end of each warfarin fill was given because changes in warfarin dosages are common.

Study cohort

The target population comprised oral anticoagulant treatment-naïve NVAF patients with their first prescription for either dabigatran (either FDA-approved dose) or warfarin between October 1, 2010 and July 31, 2012 (the index date). To be eligible, patients had to be aged 18 to 89 years at index date, to have had ≥ 1 AF diagnosis at index date or within the baseline period, and to have been continuously enrolled in the health plan during the baseline period. The DoD database includes patients in worldwide locations who receive comprehensive health care coverage. Patients have no barriers to care based on out-of-pocket costs. Patients were excluded if they had a diagnosis of hyperthyroidism during the baseline period, ≥ 1 claim with a diagnosis of cardiac surgery, pericarditis, myocarditis, or pulmonary embolism (PE) within three months of the first diagnosis of AF (to exclude patients with transient causes of AF), or ≥ 1 medical claim for valvular heart disease during the baseline period (see Suppl. Tables 1 and 2 for *International Classification of Diseases, Ninth Edition* (*ICD-9*) codes of conditions leading to exclusion, available online at www.thrombosis-online.com).

Outcome measures

Study outcomes were identified by *ICD-9* codes (see Suppl. Material, available online at www.thrombosis-online.com) for inpatient admitting and primary inpatient diagnosis codes on the inpatient claim. Only one study outcome was assigned per hospitalisation. In case of discrepancy, where two different study outcomes of interest were recorded in the admitting and primary inpatient diagnoses, the primary inpatient diagnosis code was used.

The primary effectiveness outcome was occurrence of stroke (both haemorrhagic and ischaemic), and the primary safety outcome was major bleeding (defined by *ICD-9* code in the primary code position). Secondary outcomes were occurrence of ischaemic stroke, haemorrhagic stroke, major intracranial bleeding, major extracranial bleeding, major gastrointestinal (GI) bleeding (major upper GI bleeding, major lower GI bleeding), major urogenital bleeding, major other bleeding, transient ischaemic attack,

myocardial infarction (MI), venous thromboembolism, deep-vein thrombosis, PE, and death (all-cause). All were assessed during the post index follow-up period.

Table 1: Demographic and clinical characteristics at baseline and duration of follow-up, with and without propensity score matching (n, [%], except where noted).

Statistical methods

To reduce potential bias, dabigatran and warfarin study groups were established using propensity score matching (PSM). The probability (propensity) of being treated with dabigatran was calculated based on baseline characteristics of each patient. Thus, two patients with a similar propensity score, one in the dabigatran group and the other in the warfarin group, would both have similar probability of being treated with dabigatran. Univariate analyses of associations between each derived baseline characteristic and the prescribed treatment were run, and baseline characteristics that were significant predictors of treatment were combined and used to select the final multivariate propensity score model. Backwards selection at a statistical significance of 0.05 was used in the multivariate model to select final baseline characteristics for the propensity score model. The variables selected for the model that were significant predictors of treatment included age, year of treatment, Charlson Comorbidity Index (CCI), baseline comorbidities, baseline use of other drugs, and provider specialty. Older age at index, an earlier index date, a larger baseline CCI, presence of baseline comorbidities, and not being treated by a cardiologist within five days before index date were predictors of being treated with warfarin. Younger age at index, a later index date, a lower baseline CCI, absence of baseline comorbidities, and being treated by a cardiologist within five days of index date were predictors of being treated with dabigatran. Propensity scores of patients in the dabigatran and warfarin groups were randomly matched to within a caliper of 0.20 of the standard deviation (SD) of the scores.

Baseline characteristics were described for warfarin and dabigatran groups using standard summary statistics before and after PSM. Categorical variables were compared using Chi-square tests, while continuous variables were compared using t-tests if the distribution was approximately normal and using Wilcoxon tests if not. A conventional alpha of 0.05 and two-tailed level of significance were used.

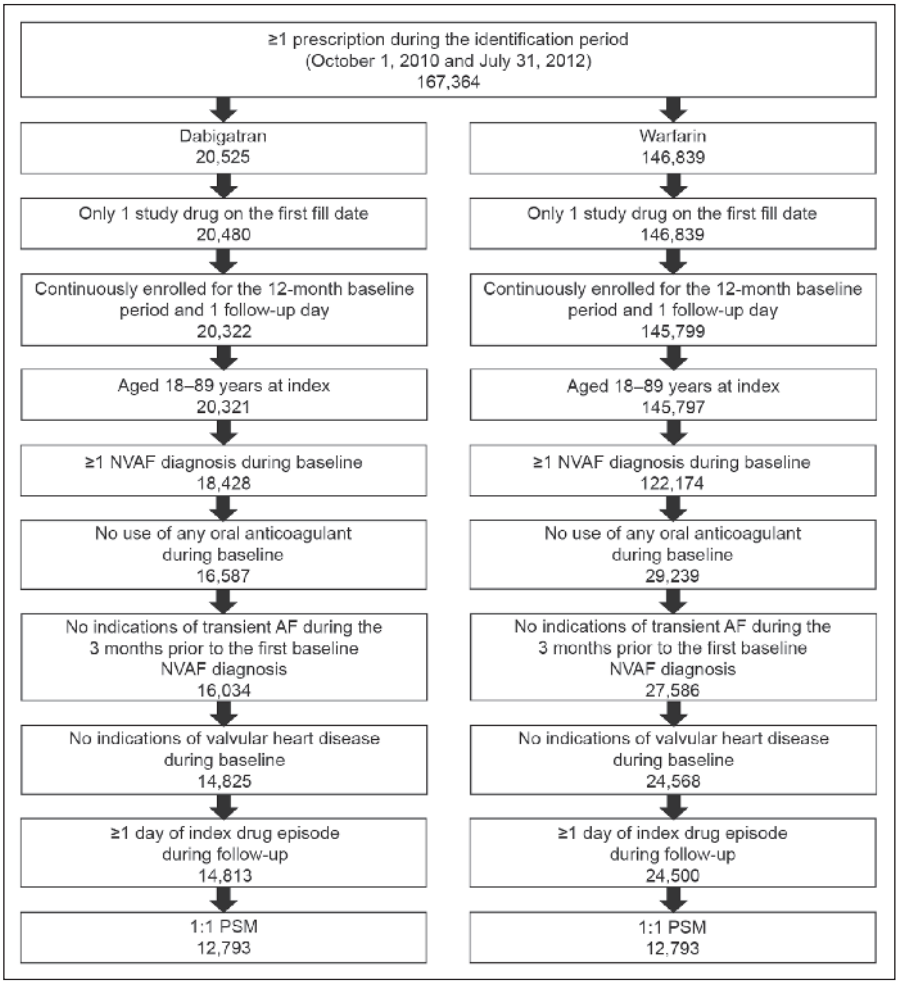

Figure 1: Overview of patient numbers by inclusion criteria. AF, atrial fibrillation; NVAF, non-valvular AF; PSM propensity score matching.

	Before Propensity Score Matching			After Propensity Score Matching		
	Dabigatran (n=14,813)	Warfarin (n=24,500)	P value Dabigatran vs Warfarin	Dabigatran (n=12,793)	Warfarin (n=12,793)	P value Dabigatran vs Warfarin
Age						
Mean, years (SD)	73.1 (9.6)	74.5 (9.2)	<0.0001	73.8 (9.3)	74.0 (9.0)	0.075
Gender						
Female	6057 (40.9)	10,317 (42.1)	0.017	5277 (41.2)	5253 (41.1)	0.76
Male	8756 (59.1)	14,183 (57.9)		7516 (58.8)	7540 (58.9)	
Baseline comorbidity						
Coronary artery disease	2708 (18.3)	6192 (25.3)	<0.0001	2530 (19.8)	2477 (19.4)	0.4
Ischaemic stroke	497 (3.4)	1332 (5.4)	<0.0001	476 (3.7)	427 (3.3)	0.097
TIA	243 (1.6)	514 (2.1)	0.0014	222 (1.7)	200 (1.6)	0.28
Heart failure	1694 (11.4)	4588 (18.7)	<0.0001	1645 (12.9)	1572 (12.3)	0.17
Hypertension diagnosis*	5381 (36.3)	11,668 (47.6)	<0.0001	4906 (38.3)	4753 (37.2)	0.048
Hypertension diagnosis or treatment†	14,228 (96.1)	23,649 (96.5)	0.015	12,349 (96.5)	12,239 (95.7)	0.54
Kidney disease	1514 (10.2)	4839 (19.8)	<0.0001	1499 (11.7)	1425 (11.1)	0.15
Diabetes mellitus	2,014 (13.6)	4,824 (19.7)	<0.0001	1,912 (14.9)	1,843 (14.4)	0.22
Baseline use of other medications						
Diuretics	6337 (42.8)	12,232 (49.9)	<0.0001	5842 (45.7)	5793 (45.3)	0.54
Other antihypertensives	1422 (9.6)	2958 (12.1)	<0.0001	1320 (10.3)	1258 (9.8)	0.2
Antidiabetics	3464 (23.4)	6481 (26.5)	<0.0001	3132 (24.5)	3197 (25.0)	0.35
Antiarrhythmics	3816 (25.8)	4987 (20.4)	<0.0001	2844 (22.2)	2814 (22.0)	0.65
Baseline Charlson Comorbidity Index						
Mean (SD)	2.5 (2.4)	3.3 (2.9)	<0.0001	2.7 (2.4)	2.7 (2.6)	0.032
Baseline stroke risk						
Mean (SD) CHA_2DS_2-VASc score	3.8 (1.7)	4.2 (1.8)	<0.0001	3.9 (1.7)	3.9 (1.7)	0.97
CHA_2DS_2-VASc score						
0 (low risk)	352 (2.4)	384 (1.6)	<0.0001	226 (1.8)	254 (2.0)	0.8
1 (intermediate risk)	1057 (7.1)	1175 (4.8)		785 (6.1)	766 (6.0)	
2–9 (high risk)	13,404 (90.5)	22,941 (93.6)		11,782 (92.1)	11,773 (92.0)	
Baseline bleeding risk						
Mean (SD) HAS-BLED score	3.4 (1.3)	3.6 (1.3)	<0.0001	3.4 (1.2)	3.4 (1.3)	0.32
HAS-BLED score						
0 (low risk)	883 (6.0)	1077 (4.4)	<0.0001	656 (5.1)	728 (5.7)	0.079
1–2 (intermediate risk)	2846 (19.2)	3648 (14.9)		2316 (18.1)	2353 (18.4)	
3–9 (high risk)	11,084 (74.8)	19,775 (80.7)		9821 (76.8)	9712 (75.9)	
Specialty of prescribing provider on index						
Cardiology	5961 (40.2)	6414 (26.2)	<0.0001	4187 (32.7)	4189 (32.7)	0.98
Other/unknown	8852 (59.8)	18,086 (73.8)		8606 (67.3)	8604 (67.3)	
Duration of follow-up, days						
Mean (SD)	297.2 (258.8)	215.5 (225.2)	<0.0001	297.3 (258.1)	217.2 (222.9)	<0.0001

AF, atrial fibrillation; SD, standard deviation; TIA, transient ischaemic attack. *Hypertension as defined by a recorded diagnosis during the baseline period. †Hypertension as defined by a recorded diagnosis or concomitant therapy with anti-hypertensive or cardiac agents (beta blockers, calcium-channel blockers, diuretics or other anti-hypertensives).

Event rates (with 95% confidence intervals [CIs]) for each outcome were calculated on an on-treatment basis as total number of patients in each group who had the outcome during follow-up, divided by total person-time of that event for the group. Person-time was calculated separately for each outcome; person-time consisted of the entire follow-up period for patients who did not have the outcome and the time to first occurrence for patients who did have the outcome.

To compare the occurrence of primary and secondary outcomes between dabigatran and warfarin groups, time to event was evaluated using Kaplan-Meier survival analyses. Log-rank tests were used to assess whether statistically significant differences existed between groups.

Cox proportional hazards models were used to evaluate the association between time to event and treatment, adjusting for appropriate covariates if PSM left imbalance between groups. All baseline characteristics were considered in the model. These included sex; age; baseline comorbid conditions; baseline medication use; specialty of prescribing provider of index drug closest to index date; baseline CCI; baseline stroke risk (using $CHADS_2$ and CHA_2DS_2-VASc scores, where scores of 0, 1, or 2–6 on $CHADS_2$ and scores of 0, 1, or ≥2 on CHA_2DS_2-VASc signify low, intermediate, and high risk of stroke, respectively); baseline bleeding risk (using HAS-BLED bleed risk classification, where scores of 0–1, 2, or ≥3 signify low, intermediate, and high risk of bleeding, respectively); time from AF diagnosis to index exposure; new versus previous AF diagnosis (patients with a claim for AF ≤3 months before index date classified as newly diagnosed; patients with a claim >3 months before index date classified as previously diagnosed). The variables included in the final model for each outcome were determined using backward selection at statistical significance of 0.05. Prescribed treatment was always forced as a predictor of outcome in the model. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

As an additional post-hoc sensitivity analysis, hazard ratios (HR) were also calculated for a PSM subgroup of patients with prescriptions for dabigatran 150 mg or warfarin. This subgroup included patients taking dabigatran 150 mg at index and having at least one post-index day of dabigatran 150 mg. Patients with both dabigatran 150 mg and dabigatran 75 mg at index (n=8) were excluded, and follow-up was stopped when the patient started using another oral anticoagulant, including dabigatran 75 mg.

Results

Demographic and clinical characteristics

A total of 14,813 dabigatran and 24,500 warfarin patients from the DoD database were available for PSM once inclusion and exclusion criteria had been applied (▶Figure 1). Before PSM, statistically significant differences existed between groups in almost all baseline demographic and clinical characteristics (▶Table 1). Thus, the dabigatran group was younger (mean age, 73.1 vs 74.5 years) with significantly lower levels of comorbidities than the warfarin group. In addition, the dabigatran group had a lower mean CCI (2.5 vs 3.3); mean $CHADS_2$ score (2.3 vs 2.6); and mean CHA_2DS_2-VASc score (3.8 vs 4.2) than the warfarin group. Other differences seen before PSM included speciality of prescribing provider upon index; 40% of prescribers were cardiologists in the dabigatran group compared with 26% in the warfarin group. PSM based on demographics and baseline clinical characteristics was achieved 1:1 with 12,793 matched subjects per group and resulted in two well-matched groups. Before PSM, mean [SD] duration of follow-up

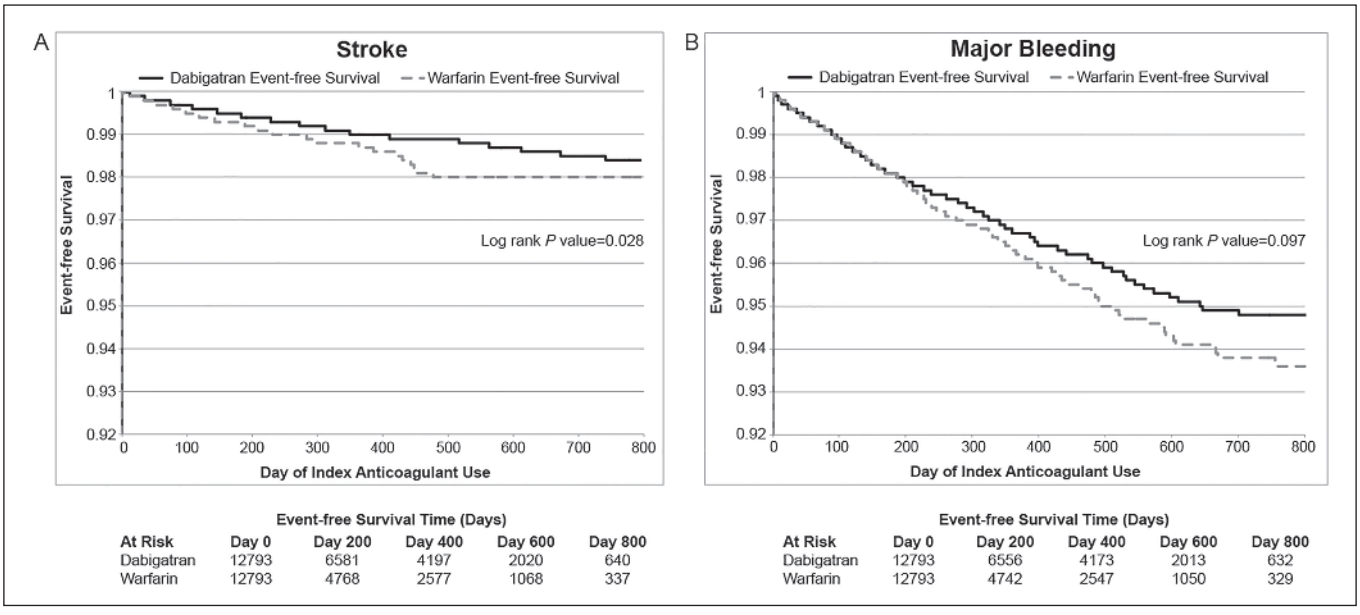

Figure 2: Time from index date to occurrence of stroke or major bleeding with dabigatran and warfarin.

Table 2: Event rates for primary and secondary outcomes in the dabigatran and warfarin groups, post-propensity score matching.

	Dabigatran (n=12,793)		Warfarin (n=12,793)	
	Patients With Given Outcome, n	Event Rate/ 100 Person years (95 % CIs)	Patients With Given Outcome, n	Event Rate/ 100 Person-years (95 % CIs)
Primary outcomes				
Stroke	95	0.92 (0.74–1.12)	100	1.32 (1.07–1.60)
Major bleeding	319	3.08 (2.76–3.44)	279	3.70 (3.28–4.16)
Secondary outcomes				
Ischaemic stroke	88	0.85 (0.68–1.04)	81	1.07 (0.85–1.33)
Haemorrhagic stroke	8	0.08 (0.03–0.15)	19	0.25 (0.15–0.39)
Major intracranial bleeding	28	0.27 (0.18–0.39)	43	0.56 (0.41–0.76)
Major extracranial bleeding	291	2.81 (2.50–3.16)	236	3.13 (2.74–3.56)
Major GI bleed	263	2.54 (2.24–2.87)	179	2.37 (2.03–2.74)
Major upper GI bleed	57	0.55 (0.42–0.71)	58	0.76 (0.58–0.99)
Major lower GI bleed	210	2.02 (1.76–2.32)	124	1.64 (1.36–1.95)
Major urogenital bleed	11	0.11 (0.05–0.19)	23	0.30 (0.19–0.45)
Major other bleed	20	0.19 (0.12–0.30)	39	0.51 (0.36–0.70)
TIA	48	0.46 (0.34–0.61)	42	0.55 (0.40–0.75)
MI	53	0.51 (0.38–0.67)	59	0.78 (0.59–1.00)
VTE	14	0.13 (0.07–0.22)	16	0.21 (0.12–0.34)
DVT	6	0.06 (0.02–0.12)	10	0.13 (0.06–0.24)
PE	8	0.08 (0.03–0.15)	6	0.08 (0.03–0.17)
Death	326	3.13 (2.80–3.49)	399	5.24 (4.74–5.78)

CI, confidence interval; DVT, deep vein thrombosis; GI, gastrointestinal; MI, myocardial infarction; PE pulmonary embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

was longer in the dabigatran (297.2 [258.8] days) than in the warfarin (215.5 [225.2] days) groups. A number (n=2,020) of dabigatran patients could not be included in the matched analysis. They were younger than the warfarin patients, and were not included for the sole reason that they did not have matches.

Following PSM, the dabigatran and warfarin groups had mean ages of 73.8 ± 9.3 and 74.0 ± 9.0 years, respectively (p=0.075). In both PSM groups, 54 % of subjects were aged ≥ 75 years, and 13 % were aged ≥ 85 years. Duration of follow-up in the PSM groups was 297.3 ± 258.1 days and 217.2 ± 222.9 days in the dabigatran and warfarin groups, respectively. Within the matched dabigatran group, 87.6 % of patients had prescriptions for the 150-mg dose on their index day (150 mg, n = 11,212; 75 mg, n = 1,573; both doses, n = 8). The overall size of the 75 mg subgroup did not meet the pre-specified protocol-specified power threshold for a separate subgroup analysis. Significant demographic and clinical differences between the pre-PSM 75 mg and 150 mg sub-groups are shown in Suppl. Table 3 (available online at www.thrombosis-online.com). Baseline demographics and clinical characteristics of a PSM subgroup comparing dabigatran 150 mg to warfarin are shown in Suppl. Table 4 (available online at www.thrombosis-online.com).

Primary and secondary outcomes

The probability of event-free survival with dabigatran (►Figure 2) was greater than with warfarin over the follow-up period for both stroke (p=0.028) and major bleeding (not significant; p=0.097).

Event rates/100 person-years over the follow-up period (after PSM) are shown in ►Table 2. Specifically, the event rate/100 person-years (95 % CI) for the primary outcome of stroke was 0.92 (0.74–1.12) for the dabigatran group and 1.32 (1.07–1.60) for the warfarin group. Patients prescribed dabigatran also experienced lower event rate/100 person-years for the primary outcome of major bleeding: 3.08 (2.76–3.44) compared with 3.70 (3.28–4.16) for warfarin. Outcome event rates were not significantly different with 45- and 60-day allowable gaps or when the method of Go et al. (12) was used in sensitivity analysis to determine duration of warfarin exposure.

HRs of primary and secondary outcomes are shown in ►Figure 3. Overall, the dabigatran group was associated with lower event and HRs of stroke, haemorrhagic stroke, major intracranial bleeding, major urogenital and other bleeding, MI, and death than the warfarin group. There was no significant difference in the HR for major GI bleeding between groups;

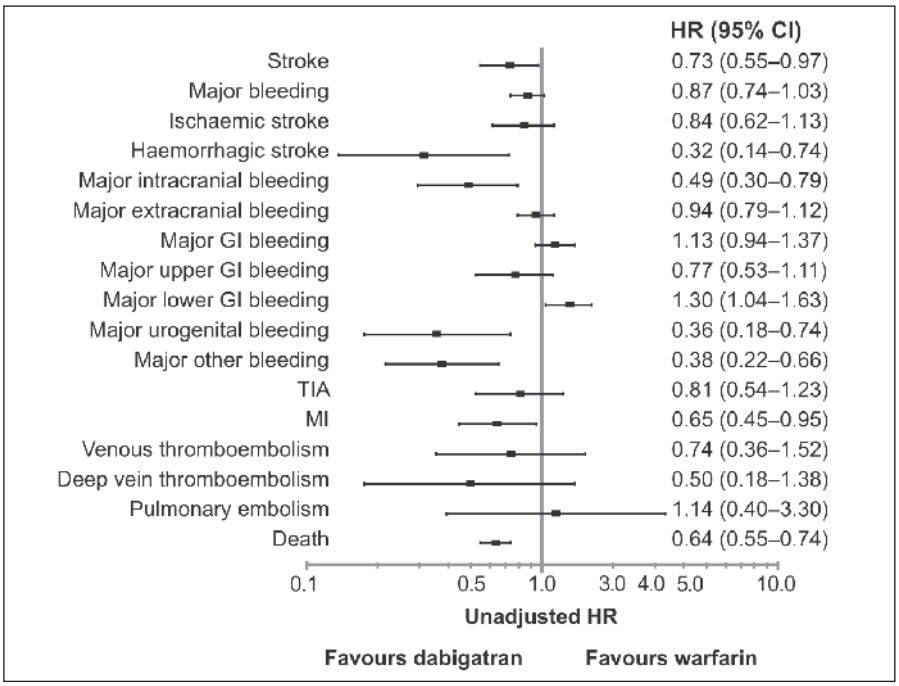

Figure 3: Hazard ratios* (95 % CIs) for primary and secondary outcomes: dabigatran versus warfarin. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischaemic attack. *Following propensity score matching, the crude (unadjusted) and adjusted hazard ratios for primary and secondary outcomes were almost all identical. Thus, only unadjusted hazard ratios are shown.

however, the HR of major lower GI bleeding was significantly higher in the dabigatran-treated patients. Due to the close matching achieved by the model, the unadjusted and adjusted HR did not differ. The adjusted HR (95 % CI) for stroke was 0.73 (0.55–0.97) for dabigatran versus warfarin. The adjusted HR (95 % CI) for major bleeding was 0.87 (0.74–1.02) for dabigatran versus warfarin.

Similar results were assessed in a subgroup analysis that compared a PSM population of patients receiving dabigatran 150 mg or warfarin (unadjusted HRs shown in Suppl. Table 5, available online at www.thrombosis-online.com). In this population, which excluded patients with dabigatran 75 mg prescriptions, the adjusted HRs for stroke and major bleeding for dabigatran 150 mg versus warfarin were 0.73 (0.55–0.96) and 0.82 (0.71–0.95).

Discussion

While there have been a number of studies of dabigatran in clinical practice (11, 13–22) this study benefits from having a generally older cohort of patients with a mean age of 73–74 years and extends the current data to a large-scale non-Medicare population that has no economic barriers to care. The recently reported Medicare study by Graham et al. (13) warrants validation in a non-Medicare population. Using data from the DoD database, prior to matching, we found significant differences in patient characteristics between groups prescribed dabigatran or warfarin. Specifically, patients prescribed dabigatran in this population were younger (mean age, 73.1 years in the dabigatran group; 74.5 years in the warfarin group) and at lower risk of stroke and bleeding than patients prescribed warfarin. Similar differences in characteristics of patients receiving dabigatran and warfarin have been reported previously using registry (21) and Medco claims data (17). Administrative data from Denmark likewise demonstrated a greater likelihood of dabigatran prescription to slightly younger patients with less comorbidity (23). In our study, differences in mean CCI, CHA_2DS_2-VASc, and HAS-BLED scores before PSM among newly diagnosed NVAF patients assigned to dabigatran and warfarin, were similar to those recorded by Schoof et al. (17).

These differences may be indicative of a more conservative strategy, whereby providers prescribe dabigatran to patients considered to be at lower risk (21). However, several potential reasons exist for differences seen between treatment groups prior to PSM; for instance, more prescribers were cardiologists for patients who received dabigatran than were for patients who received warfarin. Nonetheless, the findings simply may reflect greater levels of engagement in treatment decisions between younger, more informed patients and their prescribing providers. Additionally, a recent evaluation of newly diagnosed NVAF patients prescribed dabigatran and warfarin in the DoD dataset (11), found higher persistence rates with dabigatran than with warfarin at six months (64 % vs 41 %) and one year (50 % vs 24 %), results that may be considered consistent with more favourable outcomes and longer duration of follow-up seen with dabigatran than with warfarin in our analysis.

After PSM, dabigatran use was associated with a significantly lower HR of the primary endpoints of stroke or major bleeding compared with warfarin. Significantly lower HRs were also seen with dabigatran for secondary endpoints of ischaemic stroke, haemorrhagic stroke, major intracranial, urogenital, and other bleeding, MI, and death, but with a higher HR of major lower GI bleeding, compared with warfarin. While increased risk of GI

bleeding and decreased risk of bleeding from other sites with dabigatran compared with warfarin have been seen in other studies, the pathophysiology of this observation is unclear. Few studies have compared the sites of GI bleeding events associated with warfarin vs dabigatran therapy. Descriptive data from the RE-LY trial indicate that patients on warfarin experienced higher frequencies of upper vs lower GI bleeding (75% vs 25%, respectively), while patients on dabigatran experienced approximately equal frequencies of upper vs lower GI bleeds (53% vs 47%, respectively) regardless of dose (24). In light of these results, the current finding of increased major lower GI bleeding versus no difference in major upper GI bleeding among dabigatran versus warfarin treated subjects should be considered hypothesis generating.

The event rates/100 person-years for stroke (0.92) and major bleeding (3.08) seen with dabigatran in the DoD database are similar to values of 1.5 events/100 person-years and 2.5 events/100 person-years, respectively, reported in patients treated with dabigatran in a Swedish national quality registry for anticoagulant therapy (14). Also, comparable data were reported in a recent study by Larsen et al. from the Danish National Prescription Registry, which included vitamin K antagonist-naïve patients prescribed either warfarin or dabigatran (22). Patients prescribed dabigatran 150 mg (n=4018) experienced lower event rates of major bleeding compared with warfarin (n=14,126: 2.2 vs 3.7 events/100 patient-years). In these same groups, intracranial bleeding was also less frequent with dabigatran 150 mg compared with warfarin (0.23 vs 0.98 events/100 patient-years), and GI bleeding event rates were 0.49 events/100 patient-years for dabigatran 150 mg and 0.58 events/100 patient-years for warfarin. Additionally, an FDA analysis of data from 134,000 Medicare patients found that among new users of oral anticoagulant drugs, dabigatran (75-mg or 150-mg doses, without stratification) was associated with a lower incidence than warfarin of ischaemic stroke (1.13 vs 1.39 events/100 person-years), intracranial haemorrhage (0.33 vs 0.96 events/100 person-years), and death (3.26 vs 3.78 events/100 person-years) (13). An increased incidence of major GI bleeding with dabigatran (3.42 events/100 person-years) compared with warfarin (2.65 events/100 person-years) was reported. A recent systematic review and meta-analysis of randomised clinical trials with NOACs (dabigatran, apixaban, rivaroxaban or edoxaban) versus warfarin found similar efficacy to warfarin in prevention of thromboembolic events (24). Data for dabigatran 150 mg showed a significantly higher major gastrointestinal bleeding risk versus warfarin (1.78, 1.35–2.35) but lower intracranial bleeding risks versus warfarin (0.43, 0.26–0.72) (24).

The strength of our methodology is shown in the reduction of significant differences in baseline demographic categories and clinical characteristics in the post-PSM populations. Pre-PSM, the dabigatran and warfarin cohorts demonstrated statistically significant differences in a number of their baseline characteristics. Post-PSM, confounding differences were largely eliminated. Additionally, a PSM subgroup analysis which excluded patients receiving the 75 mg dose of dabigatran found nearly identical HRs as in the cohort that included both FDA-approved doses, thereby delivering confirmatory dose-specific (150 mg) data. Our results are consistent with what was seen in the RE-LY clinical trial (1.11 and 3.11 events/100 person-years for stroke and major bleeding, respectively) (9). The rate of each primary and secondary outcome for dabigatran versus warfarin in the DoD database analysis was similar to that seen in RE-LY, with the exception that risk of MI was lower with dabigatran in the DoD analysis described here. Although meta-analyses of clinical trials have concluded that dabigatran and oral direct thrombin inhibitors as a class may be associated with increased risk of MI (25, 26), the risk was seen to be reduced relative to warfarin in this large population of patients in clinical care. In the FDA Medicare analysis, the risk of MI was similar for dabigatran compared with warfarin (1.57 vs 1.69 events/100 person-years) (13).

Results between the DoD study and RE-LY are not directly comparable because of lack of randomisation in this study, different inclusion and exclusion criteria, lengths of follow-up, differences in event definitions (here based on *ICD-9* coding vs protocol-specified definitions with adjudication in RE-LY), and types of analysis. Also, this current analysis that attempts to assess the "real world" utilisation of dabigatran as a treatment strategy, includes patients treated with either FDA-approved dose of dabigatran within the same group, which may include some instances of off-label dosing.

A key limitation of our findings is that they are observational in nature. To minimise potential bias that may occur in observational studies, only patients new to oral anticoagulation were included in this study, and PSM was conducted. Possible limitations include unrecognized confounding due to characteristics not measured or included in the PSM, coding errors of omission or commission, and incomplete claims. Although PSM resulted in two clinically similar groups, the pre-PSM populations were significantly different with regard to several clinical characteristics. It is possible that differences that affected the propensity for prescribing either dabigatran or warfarin may not have been fully adjusted for in the PSM. Additionally, the study did not include access to INR control data for prothrombin time or data for mean time in therapeutic

What is known about this topic?

- There have been a number of studies of dabigatran in patients with NVAF in clinical practice based on US Medicare data.
- These studies have observed lower incidences of ischaemic stroke and intracranial haemorrhage with dabigatran versus warfarin, but higher incidence of GI bleeding with dabigatran.
- The Medicare study published in 2014 by Graham et al. used propensity-score matching to evaluate those endpoints.

What does this paper add?

- This study extends the current data to a large-scale non-Medicare population without economic barriers to care.
- The present data confirm that compared with warfarin, dabigatran treatment was associated with a lower risk of stroke and most outcomes measured, but more frequent major lower GI bleeding.

range with warfarin treatment. These data would have provided confirmation of the level of anticoagulation in the warfarin population and allowed for a more rigorous comparison to the dabigatran population as was done in the RE-LY trial. Nonetheless, the findings are real-world data, and DoD patients receiving OACs are treated in dedicated anticoagulation clinics. They are, therefore, likely to have good INR control. Finally, the analysis was performed in an on-treatment fashion in order to most directly assess outcomes attributed to drug exposure. Changes in therapy or discontinuation for reasons not captured as coded bleeding events are a limitation of this on-treatment analysis.

Conclusions

The results of this large, observational study are generally consistent with those of the RE-LY trial, showing that the effectiveness of dabigatran seen in clinical trials also may be achieved in a broad, heterogeneous older population receiving routine clinical care.

Acknowledgements

The authors acknowledge Dorothee Bartels and Kristina Zint, who provided insight and expertise to the protocol that greatly assisted this research study. This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Editorial assistance was provided by Aideen Young and Thomas Gegeny of Envision Pharma Group, which was contracted by BIPI for these services. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, were fully responsible for all content and editorial decisions, and were involved at all stages of this manuscript's development. The authors received no compensation related to the development of the manuscript.

Conflicts of interest

JS is an employee of Boehringer Ingelheim Pharmaceuticals, Inc (BIPI), which funded this research. KS was an employee of BIPI at the time this study was performed. JC, KF, and MR are employees of Evidera, which was compensated by BIPI for conducting the data analyses. TV serves on a speaker bureau for BIPI and is compensated for such activity.

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