

Discontinuation risk comparison among 'real-world' newly anticoagulated atrial fibrillation patients: Apixaban, warfarin, dabigatran, or rivaroxaban

Lip, Gregory Y. H.; Pan, Xianying; Kamble, Shital; Kawabata, Hugh; Mardekian, Jack; Masseria, Cristina; Phatak, Hemant

DOI:

[10.1371/journal.pone.0195950](https://doi.org/10.1371/journal.pone.0195950)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Lip, GYH, Pan, X, Kamble, S, Kawabata, H, Mardekian, J, Masseria, C & Phatak, H 2018, 'Discontinuation risk comparison among 'real-world' newly anticoagulated atrial fibrillation patients: Apixaban, warfarin, dabigatran, or rivaroxaban', *PLoS ONE*, vol. 13, no. 4, e0195950. <https://doi.org/10.1371/journal.pone.0195950>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

RESEARCH ARTICLE

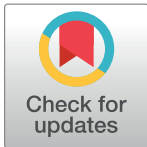
Discontinuation risk comparison among ‘real-world’ newly anticoagulated atrial fibrillation patients: Apixaban, warfarin, dabigatran, or rivaroxaban

Gregory Y. H. Lip^{1,2☯*}, Xianying Pan^{3☯}, Shital Kamble^{4☯}, Hugh Kawabata^{3☯}, Jack Mardekian^{5☯}, Cristina Masseria^{5☯}, Hemant Phatak^{4☯}

1 University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom, **2** Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, **3** Center for Observational Research and Data Science, Bristol-Myers Squibb Company (BMS), Princeton, New Jersey, United States of America, **4** Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb Company (BMS), Princeton, New Jersey, United States of America, **5** Outcomes & Evidence, Patient & Health Impact, Pfizer Inc., New York, New York, United States of America

☯ These authors contributed equally to this work.

* g.y.h.lip@bham.ac.uk



OPEN ACCESS

Citation: Lip GYH, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, et al. (2018)

Discontinuation risk comparison among ‘real-world’ newly anticoagulated atrial fibrillation patients: Apixaban, warfarin, dabigatran, or rivaroxaban. PLoS ONE 13(4): e0195950. <https://doi.org/10.1371/journal.pone.0195950>

Editor: Pablo Garcia de Frutos, Institut d'Investigacions Biomediques de Barcelona, SPAIN

Received: November 21, 2017

Accepted: April 3, 2018

Published: April 30, 2018

Copyright: © 2018 Lip et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data for these analyses were made available to the authors by third-party license from Truven MarketScan, a commercial data provider in the US, and BMS (who have a license for analysis of the Truven MarketScan data). As such, the authors cannot provide the raw data themselves. Other researchers could access the data by purchase through Truven MarketScan; and the inclusion criteria specified in the Methods section would allow them to identify the same cohort of patients

Abstract

Discontinuation of oral anticoagulants may expose non-valvular atrial fibrillation (NVAF) patients to an increased risk of stroke. This study describes the real-world discontinuation rates and compared the risk of drug discontinuation among NVAF patients initiating apixaban, warfarin, dabigatran, or rivaroxaban. This retrospective cohort study evaluated newly-anticoagulated NVAF patients in the MarketScan[®] data population from 01/01/2012 through 12/31/2014. Discontinuation was defined as a lack of subsequent prescription of the index drug within 30 days after the last supply day of the last prescription. A Cox model was used to estimate the hazard ratio (HR) of discontinuation, adjusted for age, sex, and comorbidities. Among 45,361 eligible NVAF patients, 15,461 (34.1%) initiated warfarin; 7,438 (16.4%) apixaban; 4,661 (10.3%) dabigatran; and 17,801 (39.2%) initiated rivaroxaban treatment. Compared to warfarin, patients who initiated dabigatran (adjusted HR [aHR]: 0.84, 95% confidence interval [CI]: 0.80–0.87, P<0.001), rivaroxaban (aHR: 0.70, 95% CI: 0.68–0.73, P<0.001), or apixaban (aHR: 0.57, 95% CI: 0.55–0.60, P<0.001) were 16%, 30%, and 43% less likely to discontinue treatment, respectively. When compared to apixaban, patients who initiated dabigatran (aHR: 1.46, 95% CI: 1.38–1.54, P<0.001) or rivaroxaban (aHR: 1.23, 95% CI: 1.17–1.28, P<0.001) were more likely to discontinue treatment. Among newly-anticoagulated NVAF patients in the real-world setting, initiation on rivaroxaban, dabigatran, or apixaban was associated with a significantly lower risk of discontinuation compared to warfarin. When compared to apixaban, patients who initiated treatment with warfarin, dabigatran, or rivaroxaban were more likely to discontinue treatment.

the authors used for these analyses. Interested individuals may see <http://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases> for more information on accessing Truven MarketScan data. The authors confirm that no authors had special privileges to access data from Truven MarketScan via third-party license, and that other researchers would be able to access the data in the same manner as the authors.

Funding: This study was sponsored by Bristol-Myers Squibb Company, Princeton, NJ, USA and Pfizer Inc., New York, New York, USA. The funder provided support in the form of salaries for authors XP, SK, HK, JM, CM, HM, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Gregory YH Lip has served as a consultant for Bayer/Janssen, Merck, Sanofi, Bristol-Myers Squibb Company/Pfizer Inc., Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim, and has been on the speakers' bureau for Bayer, Bristol Myers Squibb Company/Pfizer Inc., Boehringer Ingelheim, Daiichi-Sankyo, and Medtronic. Ms. Pan, Dr. Kamble, and Dr. Kawabata are employees of Bristol-Myers Squibb Company with ownership of stocks in Bristol-Myers Squibb Company. Drs. Masseria and Mardekian are employees of Pfizer Inc, with ownership of stocks in Pfizer Inc. Dr. Phatak was an employee of Bristol-Myers Squibb Company at the time of research and has ownership of stocks in Bristol-Myers Squibb Company. The authors have indicated that they have no other conflicts of interest regarding the content of this article. There are no patents, products in development, or marketed products to declare. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Introduction

While warfarin is highly effective for preventing stroke in patients with atrial fibrillation (AF), there is significant inter- and intra-patient variability in dose requirements, thus necessitating regular anticoagulation monitoring. Warfarin is also associated with many diet and drug interactions and can be associated with a significant rate of major bleeding, particularly intracranial hemorrhage [1,2]. Given these difficulties, many at-risk AF patients do not receive warfarin or receive an inadequate dose, and often discontinue therapy [1,2]. As a result, approximately 30–50% of patients have been undertreated with either suboptimal warfarin treatment, aspirin, or no anticoagulation [3]. In recent years, 4 non-Vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have been approved in the United States for stroke prevention in NVAF patients. The NOACs have advantages over warfarin in that there is no need for regular International Normalized Ratio (INR) monitoring, and there are fewer drug and food interactions. In clinical trials assessing warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban, all have been shown to be safe and effective [4–7]. Among all NOACs approved for non-valvular AF (NVAF), apixaban is the only drug that has shown, in its respective clinical trial(s), to have a significantly lower discontinuation rate than warfarin (or aspirin) possibly due to its significantly better safety and tolerability profile [6,8,9]. Due to the moderate half-life of NOACs, it is important for patients to continue to take medications daily, as indicated. For both warfarin and NOACs, drug discontinuation and missing doses (ie, lower adherence) may expose AF patients to an increased risk of stroke. Consequently, studies of discontinuation and adherence associated with NOACs are important in understanding treatment patterns and associated gaps [10,11,12]. It would be important to investigate discontinuation rates and time to discontinuation associated with various NOACs to understand the ability of patients to continue long-term NOAC use in real-world settings. The objective of this study was to describe the 'real-world' discontinuation rates and compare the risk of drug discontinuation among patients initiating apixaban, dabigatran, rivaroxaban, and warfarin. For the purposes of this analysis, there were insufficient real-world data available for edoxaban in the United States.

Methods

A retrospective cohort study was conducted using the Truven MarketScan[®] Commercial Claims & Encounters and Medicare Supplemental & Coordination of Benefits database (January 2012 through December 2014) to evaluate the discontinuation rates among AF patients who initiated apixaban, warfarin, dabigatran, or rivaroxaban treatment [13]. The database includes health insurance claims for over 60 million employees, spouses, retirees, and their dependents, enrolled in employer-sponsored commercial and Medicare advantage plans. The geographical distribution is approximately the same as the US population distribution. The database includes fully-integrated health information, including inpatient and outpatient health care resource utilization and detailed drug information. The pharmaceutical claims file includes complete records of prescriptions, including mail-order or card program prescription drug claims [13].

NVAF patients aged ≥ 18 years (identified based on presence of at least 1 claim for a primary or secondary diagnosis of AF in the inpatient or outpatient setting using ICD-9-CM code 427.31 or 472.32) with a 1-year baseline period with continuous health plan enrollment were included if they were newly prescribed oral anticoagulants from January 1, 2013 through December 31, 2014 [14]. The ICD-9 codes have been validated for identifying AF patients with a median positive predictive value of 89% [14]. In other words, a contemporary cohort of NOAC and warfarin initiators without prior oral anticoagulant treatment during the 1-year

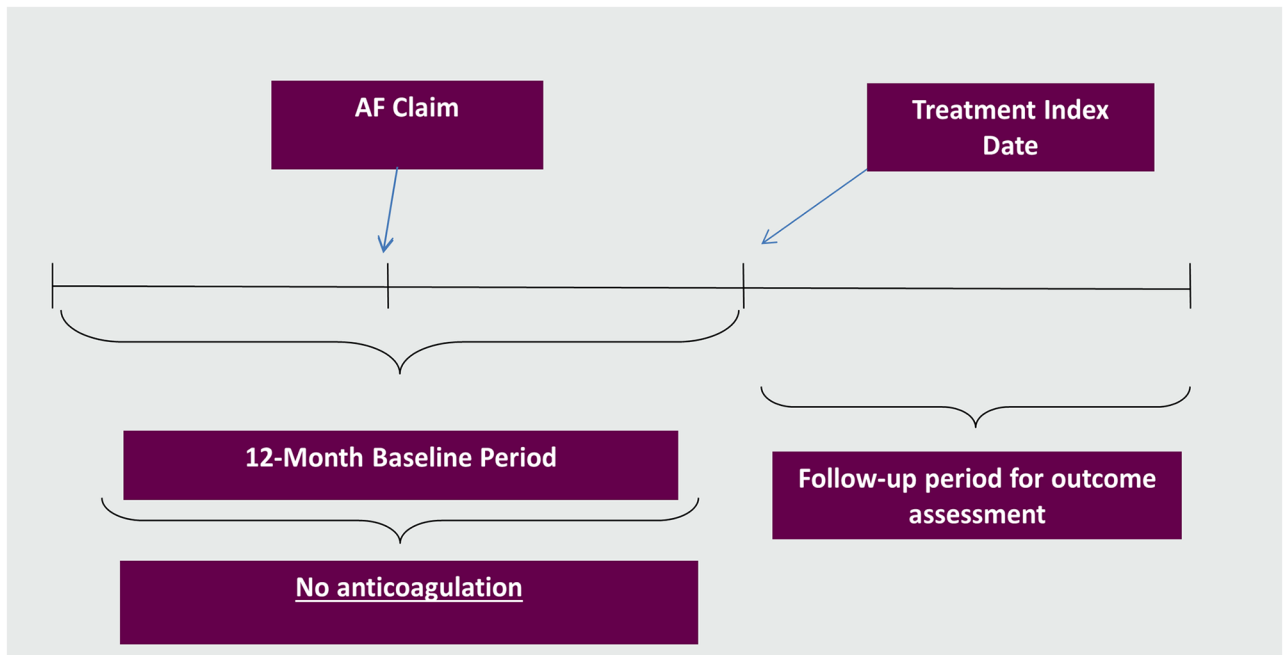


Fig 1. Study period depiction. Study period for patients initiating apixaban, dabigatran, rivaroxaban, and warfarin. AF: atrial fibrillation.

<https://doi.org/10.1371/journal.pone.0195950.g001>

baseline period was selected for this study. The index drug was defined as the first anticoagulation treatment prescribed to patients included in the study. The index date was defined as the first index drug prescription date, after NVAF diagnosis. The index date is depicted in Fig 1.

Patients with claims including ICD-9-CM diagnosis codes for transient AF (pericarditis, hyperthyroidism, thyrotoxicity), valvular heart disease, venous thromboembolism, cardiac surgery, or pregnancy during the baseline period (any time prior to or on the index date) were excluded (Fig 2; S1 Table).

Discontinuation was defined as a gap in therapy when a subsequent prescription for the index treatment occurred >30 days, plus the days supply of the previous prescription [12]. Patients who did not discontinue treatment were followed until the date of a switch to another anticoagulant, end of the study period, inpatient death, or interruption in continuous health plan enrollment, whichever occurred earliest. A sensitivity analysis was completed by changing the discontinuation gap to 60 days and 90 days.

A second sensitivity analysis was also performed. Due to varying mean length of follow-up across treatment cohorts, only patients who had at least 100 days of follow-up were included, in order to assess the robustness of the estimated risk of discontinuation.

In the study population, categorical and continuous variables were compared across treatments using the Pearson chi-square test and the Wilcoxon rank-sum test, respectively. The proportions of patients discontinuing therapy during the study follow-up period were computed as the number of patients who discontinued treatment divided by the total number of patients initiating the treatment within the study period. The cumulative incidence of discontinuation was presented using Kaplan–Meier curves. A Cox proportional hazards model was used to estimate the hazard ratios (HRs) of discontinuation for each drug compared to apixaban, adjusted for a pre-specified set of baseline demographic and clinical factors including age, sex, embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart



Fig 2. Patient selection criteria. Study population flow chart with inclusion and exclusion criteria used to select 45,361 patients. NOAC: non-vitamin K antagonist oral anticoagulant; VTE: venous thromboembolism.

<https://doi.org/10.1371/journal.pone.0195950.g002>

failure, coronary artery disease, diabetes mellitus, hypertension, renal disease, myocardial infarction, history of stroke, or transient ischemic attack, and history of bleeding (S1 Table).

As warfarin is the standard of care, we have analyzed and presented the primary results using warfarin as a reference comparator. Lower discontinuation rates were observed for NOACs in real-world studies and clinical trials; therefore, we also analyzed apixaban as a reference cohort to understand the discontinuation risk associated with NOACs and warfarin in

the real-world setting. All analyses were performed with SAS System version 9.2. An *a priori* significance level of 0.05 was used for the purposes of these analyses.

Results

Among 45,361 patients, 15,461 (34.1%) initiated warfarin treatment with a mean (SD) follow-up of 164 (\pm 162) days; 7,438 (16.4%) initiated apixaban with a mean follow-up of 148 (\pm 138) days; 4,661 (10.3%) initiated dabigatran with a mean follow-up of 177 (\pm 179) days; and 17,801 (39.2%) patients initiated rivaroxaban with a mean follow-up of 176 (\pm 171) days (Table 1). Approximately 60% of patients in each treatment group were male. The mean age of warfarin, apixaban, dabigatran, and rivaroxaban patients was 71.7 ± 12.0 , 68.5 ± 12.4 , 66.5 ± 12.4 , and

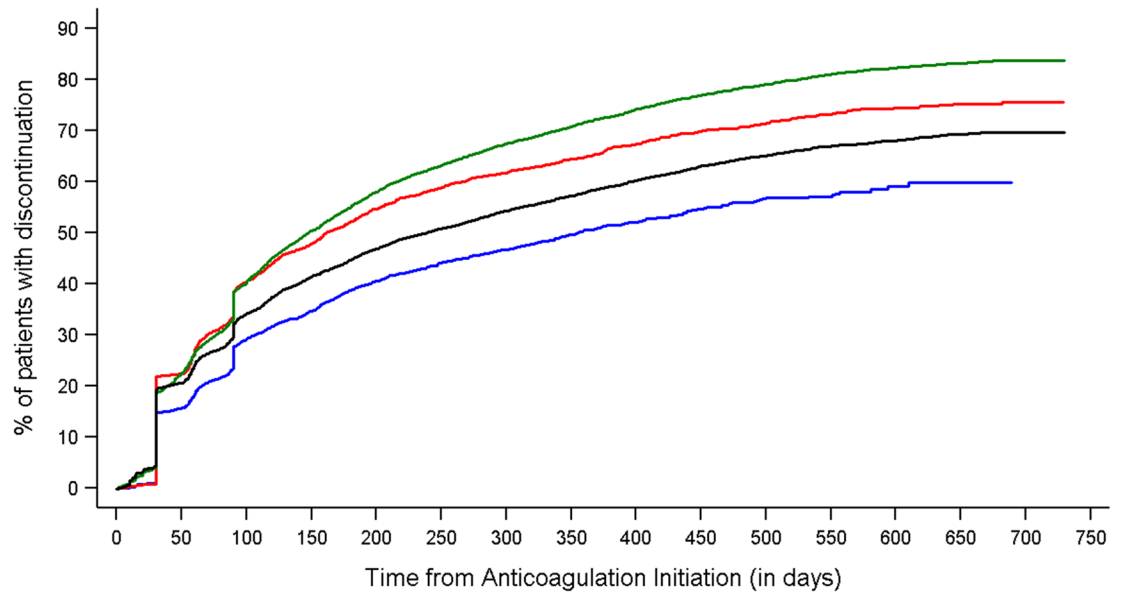
Table 1. Baseline patient characteristics and treatment follow-up period.

	Apixaban (n = 7,438)		Dabigatran (n = 4,661)		Rivaroxaban (n = 17,801)		Warfarin (n = 15,461)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Age	68.5	12.4	66.5	12.4	67.1	12.3	71.7	12.1
18–64	3111	41.8	2234	47.9	8245	46.3	4845	31.3
65–74	1805	24.23	1096	23.5	4208	23.6	3595	23.3
75+	2522	33.9	1331	28.6	5348	30.0	7021	45.4
Sex								
Male	4566	61.4	3028	65.0	11310	63.5	9254	59.9
Female	2872	38.6	1633	35.0	6491	36.5	6207	40.2
Embolic or Primary Ischemic Stroke	523	7.0	259	5.6	1056	5.9	1551	10.0
Dyspepsia or Stomach Discomfort	1082	14.6	564	12.1	2548	14.3	2470	16.0
Congestive Heart Failure	1454	19.6	873	18.7	3293	18.5	4021	26.0
Coronary Artery Disease	2410	32.4	1283	27.5	5112	28.7	5305	34.3
Diabetes	2108	28.3	1269	27.2	4802	27.0	4987	32.3
Hypertension	5585	75.1	3253	69.8	12690	71.3	11334	73.3
Renal Disease	638	8.6	333	7.1	1398	7.9	2242	14.5
Myocardial Infarction	469	6.3	251	5.4	1089	6.1	1378	8.9
History of Stroke or TIA	754	10.1	413	8.9	1574	8.8	2061	13.3
History of Bleeding	1012	13.6	536	11.5	2421	13.6	2800	18.1
CHA ₂ DS ₂ -VAsC Score*	2.8	1.6	2.6	1.7	2.6	1.7	3.2	1.7
0	514	6.9	485	10.4	1650	9.3	766	5.0
1	1222	16.4	908	19.5	3401	19.1	1809	11.7
2	1644	22.1	1027	22.0	3884	21.8	2750	17.8
≥ 3	4058	54.6	2241	48.1	8866	49.8	10136	65.6
Charlson Comorbidity Index Score	1.8	2.0	1.6	1.9	1.7	2.0	2.3	2.3
0	2244	30.2	1631	35.0	6117	34.4	3741	24.2
1	1899	25.5	1201	25.8	4468	25.1	3434	22.2
2	1270	17.1	729	15.6	2721	15.3	2499	16.2
≥ 3	2025	27.2	1100	23.6	4495	25.3	5787	37.4
Treatment Follow-up (in days)	148	138	177	178	175	171	164	162
Median	95	-	100	-	111	-	101	-
IQR	36–215	-	30–255	-	35–261	-	40–233	-

SD: Standard Deviation; TIA: Transient Ischemic Attack; IQR: Interquartile Range.

*The CHA₂DS₂-VAsC score was calculated as the sum of points associated with each of the following attributes: congestive heart failure (1 point), hypertension (1 point), age ≥ 75 (2 points), diabetes (1 point), prior stroke or TIA (2 points), vascular disease (1 point), age 65–74 (1 point), female (1 point).

<https://doi.org/10.1371/journal.pone.0195950.t001>



N at risk																
Apixaban	7438	5253	3619	2742	2049	1490	1064	735	534	346	224	142	61	16	0	0
Dabigatran	4661	3332	2336	1860	1460	1198	986	785	626	499	401	316	224	132	54	0
Rivaroxaban	17801	12714	9368	7396	5875	4702	3654	2799	2204	1688	1284	938	642	380	137	0
Warfarin	15461	11110	7841	5881	4546	3572	2748	2050	1551	1192	928	691	507	333	131	0

— Apixaban — Dabigatran — Rivaroxaban — Warfarin

Fig 3. Cumulative incidence of discontinuation among newly anticoagulated non-valvular atrial fibrillation patients. (Upper panel) Cumulative incidence of discontinuation during the follow-up period. The unadjusted cumulative incidence of discontinuation was lower among patients initiated on apixaban compared to patients initiated on other oral anticoagulants. (Lower panel) The number of patients at risk for discontinuation at varying points during the follow-up.

<https://doi.org/10.1371/journal.pone.0195950.g003>

67.1±12.3 years, respectively. Patients initiating warfarin were older and were at higher risk in terms of the CHA₂DS₂-VASc score (3.2±1.7) and had higher mean Charlson comorbidity index (CCI) scores of 2.3±2.3 (Table 1).

Fig 3 shows the discontinuation rates of all drugs across the study period. The cumulative incidence of discontinuation at one-year was 50.5%, 64.7%, 57.8%, and 71.6% for apixaban, dabigatran, rivaroxaban, and warfarin patients, respectively. When the 60- and 90-day gap was used, the rates of discontinuation were lower but the trend was consistent (S2 Table, S2 and S3 Figs). Across the four cohorts, around 3–10% of patients switched from index OAC to another OAC during the follow-up period.

When compared to warfarin, patients who initiated dabigatran (adjusted HR [aHR]: 0.84, 95% confidence interval [CI]: 0.80–0.87), rivaroxaban (aHR: 0.70, 95% CI: 0.68–0.73, P<0.001), or apixaban (aHR: 0.57, 95% CI: 0.55–0.60, P<0.001) were 16%, 30%, and 43% less likely to discontinue treatment, respectively.

When compared to apixaban, patients who initiated warfarin (aHR: 1.74, 95% CI: 1.67–1.82, P<0.001), dabigatran (aHR: 1.46, 95% CI: 1.38–1.54, P<0.001), and rivaroxaban (aHR: 1.23, 95% CI: 1.17–1.28, P<0.001) were significantly more likely to discontinue treatment, after adjusting for baseline characteristics (Table 2 and Fig 3).

For sensitivity analysis, discontinuation was assessed among patients with at least 100 days of follow-up, given the varied mean follow-up length across treatment cohorts in the main

Table 2. Adjusted hazard ratios of discontinuation.

	Hazard Ratio*	Hazard Ratio 95% Confidence Limits		P-value	Hazard Ratio*	Hazard Ratio 95% Confidence Limits		P-value
Warfarin	1.74	1.67	1.82	<0.001	1.00 Reference			
Dabigatran	1.46	1.38	1.54	<0.001	0.84	0.80	0.87	<0.001
Rivaroxaban	1.23	1.17	1.28	<0.001	0.70	0.68	0.73	<0.001
Apixaban	1.00 Reference				0.57	0.55	0.60	<0.001

Covariates Included in Both Models Have the Same Estimates as Shown Below

	Hazard Ratio*	Hazard Ratio 95% Confidence Limits		P-value
Age (75+ as a reference category)				
18–64	1.34	1.30	1.38	<0.001
65–74	0.99	0.96	1.03	0.554
Male	1.02	0.99	1.05	0.226
Embolic or Primary Ischemic Stroke	0.96	0.88	1.05	0.394
Dyspepsia or Stomach Discomfort	1.10	1.06	1.14	<0.001
Congestive Heart Failure	0.96	0.93	0.99	0.007
Coronary Artery Disease	1.01	0.98	1.04	0.557
Diabetes	0.89	0.87	0.92	<0.001
Hypertension	0.89	0.86	0.91	<0.001
Renal Disease	1.04	0.99	1.08	0.116
Myocardial Infarction	1.05	0.99	1.11	0.093
History of Stroke or Transient Ischemic Attack	0.85	0.79	0.92	<0.001
History of Bleeding	1.12	1.08	1.16	<0.001

*Adjusted hazard ratios were estimated from a Cox proportional hazards model with factors for age, sex, embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischemic attack, and history of bleeding.

<https://doi.org/10.1371/journal.pone.0195950.t002>

analysis. This reduced the effective sample size to 13,294 patients (35.50%) initiating warfarin, 5,353 (14.29%) apixaban, 4,161 (11.11%) dabigatran, and 14,644 (39.10%) rivaroxaban.

When compared to warfarin, patients who initiated dabigatran (aHR: 0.89, 95% CI: 0.85–0.92, $P < 0.001$), rivaroxaban (aHR: 0.72, 95% CI: 0.70–0.74, $P < 0.001$), or apixaban (aHR: 0.61, 95% CI: 0.58–0.64, $P < 0.001$) were less likely to discontinue treatment (S3 and S4 Tables and Fig 3). When compared to apixaban, patients who initiated warfarin (aHR: 1.64, 95% CI: 1.57–1.71, $P < 0.001$), dabigatran (aHR: 1.45, 95% CI: 1.37–1.53, $P < 0.001$), or rivaroxaban (aHR: 1.18, 95% CI: 1.12–1.23, $P < 0.001$) were more likely to discontinue treatment (S1 and S3 Tables; Fig 1).

Discussion

When compared to those who initiated warfarin, patients who initiated dabigatran, rivaroxaban, or apixaban were less likely to discontinue treatment after adjusting for baseline characteristics. Further, when compared to apixaban, patients who initiated treatment with warfarin, dabigatran, or rivaroxaban were more likely to discontinue treatment.

This study used real-world claims data from the US population to provide critical insights regarding the risk of discontinuation in an adult NVAF population who initiated anticoagulant treatment with apixaban, warfarin, rivaroxaban, or dabigatran therapy. Importantly, these ‘real-world’ results are consistent with the clinical trial findings for the respective NOACs and

warfarin. In the ARISTOTLE trial, for example, fewer patients in the apixaban group (25.3%) compared to the warfarin group (27.5%) discontinued the study drug before the end of the study ($p = 0.001$) [6]. In the ROCKET-AF trial, the proportion of patients who permanently stopped their assigned therapy before an end-point event and before the termination date was 23.7% in the rivaroxaban group and 22.2% in the warfarin group [5]. In the RE-LY trial, the rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at 1 year and 20.7%, 21.2%, and 16.6%, respectively, at 2 years [4].

The robustness of these findings through sensitivity analysis was also assessed, which largely concurred with our primary findings by demonstrating a lower risk of discontinuation with NOAC initiation as compared to warfarin, and a higher risk of discontinuation with initiation on other anticoagulants as compared to apixaban.

Our results also confirm findings from recent 'real-world' studies. A long-term study of the different NOACs in clinical practice showed that discontinuation rates were lower for apixaban (10%) compared to dabigatran (30%) and rivaroxaban (25%; $p < 0.001$ for both) [15]. Another study of NVAf patients who initiated oral anticoagulants showed significantly higher 1-year persistence rates with apixaban (86%) and warfarin (85%) than with dabigatran (74%) or rivaroxaban (77%) [16]. Furthermore, in a propensity score-matched analysis, patients who initiated dabigatran (63%) had higher persistence rates at 1 year compared to patients who initiated warfarin (39%) [12].

Discontinuation of anticoagulation or poor adherence to thromboprophylaxis is not inconsequential. Indeed, previous studies have found that warfarin discontinuation is associated with increased risk of ischemic stroke. For example, Ewen, et al. [17] found that patients with 1 or 2 or more warfarin interruptions (defined as prescription gaps over 45 days) had higher stroke incidence than those without warfarin interruption (relative risk: 2.29; 95% CI: 1.29–4.07). Deitelzweig, et al. also found that stroke risk was higher with warfarin discontinuation than during continuous warfarin therapy (HR: 1.60; 95% CI: 1.35–1.90) [18]. Similarly, in a study by Spivey et al., discontinuation versus persistent use of warfarin was associated with increased risk of ischemic stroke (HR: 2.04; 95% CI: 1.47–2.84) and ischemic stroke or TIA (HR: 1.50; 95% CI: 1.20–1.87) [19].

The anticoagulant effect of NOACs decreases rapidly; therefore, poor adherence and treatment discontinuation may diminish the benefit of NOAC treatment [20]. A higher risk of thromboembolism was noted at the end of the double-blind trials during the transition from rivaroxaban to open-label warfarin [21]. A recent analysis from the ROCKET-AF trial showed an increased risk of stroke and non-central nervous system embolism among rivaroxaban-treated versus warfarin-treated AF patients who temporarily or permanently discontinued anticoagulation (HR: 1.50, 95% CI: 1.05–2.15) [21]. Furthermore, a longitudinal outcomes study using a national cohort from the Veterans Health Administration showed that lower adherence to dabigatran was associated with an increased risk of combined all-cause mortality and stroke (HR: 1.13, 95% CI: 1.07–1.19 per 10% decrease in proportion of days covered) [22]. However, several 'real-world' studies have demonstrated reduced or similar ischemic stroke risk among patients treated with NOACs compared with warfarin, suggesting adequate adherence to maintain the benefits of NOACs [20].

Our results are also consistent with indirect comparisons that combined data from the RELY, ROCKET-AF, and ARISTOTLE studies in relation to the discontinuation of treatment [23]. While the reasons for discontinuation, causality between any particular attribute, and discontinuation of therapy cannot be determined in this retrospective study, the safety and tolerability profile of a drug likely plays a critical role in patients' ability to use NOACs continuously. For example, a 2012 study showed the rate of discontinuation of dabigatran was 25.4%, with

dyspepsia being the most common reason for discontinuation [24]. Further, a single clinical center cross-sectional study in the United States reported that the most common reasons for discontinuation with dabigatran were adverse reactions and cost [25].

The study's strengths are that we assessed the real-world risk of discontinuation of treatment among patients initiating warfarin versus dabigatran, rivaroxaban, and apixaban using the comprehensive MarketScan[®] claims database, which incorporates all medical and pharmacy patient claims and allows for longitudinal analysis of a nationally-representative sample. The medications being studied are relatively new to the market, and this database, encompassing both commercial and Medicare beneficiaries, allows for the selection of a nationally-representative sample for this study [13].

As with any retrospective analysis, researchers are limited to only study associations between variables; additionally, as with any retrospective observational database study, there is a potential for selection bias. We conducted rigorous and thorough multivariate and sensitivity analyses for discontinuation to ensure the robustness of our findings. Baseline comorbidities (eg, presence of renal impairment) were determined by the presence of a diagnosis code in the baseline period and were not based on actual laboratory test result values or clinical assessment. As this study is an analysis of claims data, there is the potential for coding errors or missing data (ie, we must assume that patients do not have a condition if it was not coded). Additionally, refill data may not reflect actual medication use. Discontinuation rates of warfarin, as assessed by a 30-day gap in pharmacy claims, may vary more due to dose adjustments to manage fluctuation in INR values compared to NOACs. As apixaban had entered the market recently when the analysis was performed, patients treated with apixaban tended to have a shorter follow-up than those treated with warfarin.

Further analyses using propensity-matched cohorts as well as large-scale prospective studies may be necessary to understand the reasons for and predictors of discontinuation, and to examine the impact of discontinuation on clinical outcomes.

Conclusions

Among newly-anticoagulated AF patients in the real-world setting, treatment initiation with rivaroxaban, dabigatran, or apixaban was associated with a significantly lower risk of discontinuation as compared to warfarin. Treatment discontinuation risk was significantly higher among patients initiating dabigatran, rivaroxaban, or warfarin, as compared to those initiating apixaban.

Supporting information

S1 Fig. Cumulative incidence of discontinuation: With a 60-day gap.
(TIF)

S2 Fig. Cumulative incidence of discontinuation: With a 90-day gap.
(TIF)

S3 Fig. Cumulative incidence of discontinuation: Minimum 100 days follow-up.
(TIF)

S1 Table. ICD-9-CM codes for selection criteria and comorbid conditions.
(DOCX)

S2 Table. Cumulative incidence of discontinuation at 1 year.
(DOCX)

S3 Table. Patient characteristics: Minimum 100 days follow-up.
(DOCX)

S4 Table. Adjusted risk of discontinuation: Minimum 100 days follow-up.
(DOCX)

Acknowledgments

Hemant Phatak was an employee of BMS at the time of this research. The authors are grateful to Todd Durham (Pre-doctoral Fellow, Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb Company) for his editorial assistance in the preparation of this manuscript.

Author Contributions

Conceptualization: Gregory Y. H. Lip, Shital Kamble, Jack Mardekian, Cristina Masseria, Hemant Phatak.

Formal analysis: Xianying Pan, Hugh Kawabata.

Methodology: Xianying Pan, Shital Kamble, Hugh Kawabata, Jack Mardekian.

Writing – original draft: Gregory Y. H. Lip, Shital Kamble, Hemant Phatak.

Writing – review & editing: Gregory Y. H. Lip, Xianying Pan, Shital Kamble, Hugh Kawabata, Jack Mardekian, Cristina Masseria, Hemant Phatak.

References

1. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsbøll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med.* 2010; 170(16):1433–41. <https://doi.org/10.1001/archinternmed.2010.271> PMID: 20837828
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007; 146(12):857–67. PMID: 17577005
3. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med.* 2010; 123(7):638–45. <https://doi.org/10.1016/j.amjmed.2009.11.025> PMID: 20609686
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361(12):1139–51. <https://doi.org/10.1056/NEJMoa0905561> PMID: 19717844
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; 365(10):883–91. <https://doi.org/10.1056/NEJMoa1009638> PMID: 21830957
6. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; 365(11):981–92. <https://doi.org/10.1056/NEJMoa1107039> PMID: 21870978
7. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013; 369(22):2093–104. <https://doi.org/10.1056/NEJMoa1310907> PMID: 24251359
8. Phatak HM, Thomas J 3rd. Relationships between beliefs about medications and nonadherence to prescribed chronic medications. *Ann Pharmacother.* 2006; 40(10):1737–42. <https://doi.org/10.1345/aph.1H153> PMID: 16985088
9. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Serv Res.* 2012; 12:98. <https://doi.org/10.1186/1472-6963-12-98> PMID: 22510235

10. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD et al. Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J*. 2010; 159(3):331–9. <https://doi.org/10.1016/j.ahj.2009.07.035> PMID: 20211292
11. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011; 364(9):806–17. <https://doi.org/10.1056/NEJMoa1007432> PMID: 21309657
12. Zalesak M, Siu K, Francis K, Yu C, Alvrtsyan H, Rao Y. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes*. 2013; 6(5):567–74. <https://doi.org/10.1161/CIRCOUTCOMES.113.000192> PMID: 23922182
13. Adamson DM, Chang S, Hansen LG. Health research data for the real world: the MarketScan® databases. Thomson Medstat Research and Pharmaceutical Division; 2008. http://depts.washington.edu/chaseall/pdfs/white%20paper_Thomson%20Reuters%20WP%20MarketScan%20Databases%200708.pdf. Accessed July 10, 2016
14. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. Identifying atrial fibrillation from electronic medical data: a systematic review. *Pharmacoepidemiol Drug Saf*. 2012; 21(01):141–7.
15. Al-Khalili F, Lindström C. Discontinuation rates in patients with non-valvular atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants (NOACs) are mainly related to drug specific side effects and bleeding. Poster presented at: European Society of Cardiology (ESC) Congress; August 29–September 2, 2015; London.
16. Forslund R, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2016; 72(3):329–38. <https://doi.org/10.1007/s00228-015-1983-z> PMID: 26613954
17. Ewen E, Zhang Z, Simon TA, Kolm P, Liu X, Weintraub WS. Patterns of warfarin use and subsequent outcomes in atrial fibrillation in primary care practices. *Vasc Health Risk Manag*. 2012; 8:587–98. <https://doi.org/10.2147/VHRM.S34280> PMID: 23112579
18. Deitelzweig SB, Buysman E, Pinsky B, Lacey M, Jing Y, Wiederkehr D, et al. Warfarin use and stroke risk among patients with nonvalvular atrial fibrillation in a large managed care population. *Clin Ther*. 2013; 35(8):1201–10. <https://doi.org/10.1016/j.clinthera.2013.06.005> PMID: 23867114
19. Spivey C, Liu X, Qiao Y, Mardekian J, Parker RB, Phatak H, et al. Stroke associated with discontinuation of warfarin therapy for atrial fibrillation. *Curr Med Res Opin*. 2015; 31(11):2021–9. <https://doi.org/10.1185/03007995.2015.1082995> PMID: 26390258
20. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015; 17(10):1467–507. <https://doi.org/10.1093/europace/euv309> PMID: 26324838
21. Patel MR, Hellkamp AS, Lokhnygina Y, Piccini JP, Zhang Z, Mohanty S, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2013; 61(6):651–8. <https://doi.org/10.1016/j.jacc.2012.09.057> PMID: 23391196
22. Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the Veterans Health Administration. *Am Heart J*. 2014; 167(6):810–7. <https://doi.org/10.1016/j.ahj.2014.03.023> PMID: 24890529
23. Mitchell SA, Simon TA, Raza S, Jakouloff D, Orme ME, Lockhart I, et al. The efficacy and safety of oral anticoagulants in warfarin-suitable patients with nonvalvular atrial fibrillation: systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2013; 19(6):619–31. <https://doi.org/10.1177/1076029613486539> PMID: 23698729
24. Ho JC, Chang AM, Yan BP, Yu CM, Lam YY, Lee VW. Dabigatran compared with warfarin for stroke prevention with atrial fibrillation: experience in Hong Kong. *Clin Cardiol*. 2012; 35(12):E40–5. <https://doi.org/10.1002/clc.22069> PMID: 23108916
25. Jacobs A, Linn D, Sipe B, Heyerly A, Bokhart G. Evaluation of reasons for dabigatran discontinuation in a community hospital and anticoagulation clinic. *Hosp Pharm*. 2014; 49(2):115–6. <https://doi.org/10.1310/hpj4902-115> PMID: 24623863