CrossMark

Prescribing trends of atrial fibrillation patients who switched from warfarin to a direct oral anticoagulant

Zachary D. Hale[1] · Xiowen Kong[2] · Brian Haymart[2] · Xiaokui Gu[2] ·
Eva Kline-Rogers[2] · Steve Almany[3] · Jay Kozlowski[4] · Gregory D. Krol[5] ·
Scott Kaatz[5] · James B. Froehlich[2] · Geoffrey D. Barnes[2]

Abstract Direct oral anticoagulant (DOAC) agents offer several lifestyle and therapeutic advantages for patients relative to warfarin in the treatment of atrial fibrillation (AF). These alternative agents are increasingly used in the treatment of AF, however the adoption practices, patient profiles, and reasons for switching to a DOAC from warfarin have not been well studied. Through the Michigan Anticoagulation Quality Improvement Initiative, abstracted data from 3873 AF patients, enrolled between 2010 and 2015, were collected on demographics and comorbid conditions, stroke and bleeding risk scores, and reasons for anticoagulant switching. Over the study period, patients who switched from warfarin to a DOAC had similar baseline characteristics, risk scores, and insurance status but differed in baseline CrCl. The most common reasons for switching were patient related ease of use concerns (37.5%) as opposed to clinical reasons (16.5% of patients). Only 13% of patients that switched to a DOAC switched back to warfarin by the end of the study period.

Keywords Atrial fibrillation · Dabigatran · Rivaroxaban · Apixaban · DOAC · NOAC

✉ Zachary D. Hale
  Zachary.Hale@bcm.edu

1 Texas Heart Institute, CHI-Baylor St. Luke's Medical Center, 6720 Bertner Ave. MC-1-133, Houston, TX 77030, USA

2 University of Michigan Cardiovascular Center, 24 Frank Lloyd Wright Dr., Lobby A Rm 3201, Ann Arbor, MI 48106, USA

3 William Beaumont Hospital, 4600 Investment Drive Suite 200, Troy, MI 48098, USA

4 Huron Valley Sinai Hospital, 1 William Carls Drive, Commerce, MI 48382, USA

5 Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, MI 48202, USA

Introduction

After decades with warfarin as the only anticoagulant for stroke prevention in non-valvular atrial fibrillation (AF), four new direct oral anticoagulants (DOACs) have become available since 2010. DOACs offer many potential advantages over warfarin including rapid onset of action, no required therapeutic blood level monitoring, less interactions with food and medications, no dosing adjustments, and fewer lifestyle modifications [1–5]. As a result, the clinical use of DOACs has been increasing in the United States and Canada, and accounted for over half of new anticoagulant starts by the end of 2014, and appears to be rising [6–10]. With several anticoagulant options, physicians and patients appear to have an increasingly collaborative role in medication selection [11]. However, the characteristics of the AF patients that switch from warfarin to a DOAC, their reasons for switching, and whether or not they switch back to warfarin, are not well studied.

We hypothesize that warfarin-treated patients with AF who elect to change therapy are younger and with fewer comorbidities as compared to those patients who choose to remain on warfarin. To test this hypothesis, we conducted a retrospective analysis of AF patients from six diverse anticoagulant clinics participating in the Michigan Anticoagulation Quality Improvement Initiative (MAQI²). Additionally, we abstracted data from clinic and hospital visits

to monitor for any patients who transitioned from a DOAC back to warfarin.

Methods

Michigan anticoagulation quality improvement initiative (MAQI[2])

MAQI[2] is a Blue Cross Blue Shield of Michigan/Blue Care Network (BCBSM/BCN) quality improvement collaborative [12]. This collaborative of six health system anticoagulation clinics was formed in 2008, with the focus to improve anticoagulation patient safety, healthcare quality, and promoting collaboration on outcomes projects across the state of Michigan. Patients newly enrolling in each center's anticoagulation clinic are randomly selected for chart abstraction into the MAQI[2] database. Trained data abstractors collect de-identified patient care data from anticoagulation clinic visits and supplement that data with both outpatient and hospitalization records. BCBSM/BCN provides funding for data collection and quality improvement work, but does not participate in data analysis or manuscript editing. The MAQI[2] project was reviewed and approved by the IRB at the coordinating center (University of Michigan) and each participating site.

Patient selection

Between January 2010 and June 2015, all non-valvular AF patients in the MAQI[2] database who were treated with warfarin were eligible for inclusion in this study. Exclusion criteria include patients on anticoagulation solely for indications other than AF (e.g. venous thromboembolism, mechanical valve replacement), patients who switched to non-DOAC warfarin alternatives (e.g. enoxaparin, clopidogrel), and patients with fewer than one follow up encounter. 3873 patients met selection criteria (Fig. 1). These patients were divided into two cohorts: (1) patients who switched from warfarin therapy to DOAC therapy, and (2) patients who remained exclusively on warfarin therapy.

Data collection

Demographic, comorbidity, INR levels, insurance status, and co-administered medication data were collected at the time of enrollment in the anticoagulation clinic. HAS-BLED and CHA_2DS_2-VASc risk scores, and time in therapeutic range were calculated using the baseline characteristics data to measure patient risk and warfarin INR control [11, 13, 14]. Chronic kidney disease (CKD) status, defined as creatinine clearance (CrCl) <60 mL/min, was obtained from review of the medical record, and laboratory data
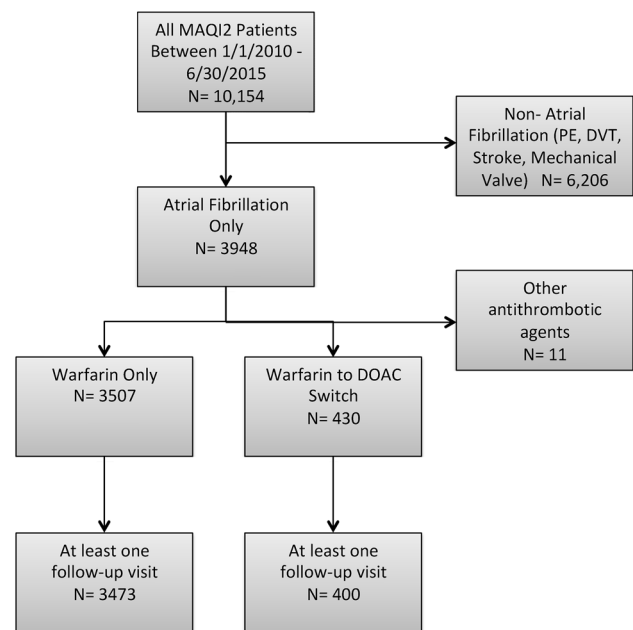

Fig. 1 Patient selection algorithm

were used to calculate the estimated CrCl with the Crockroft-Gault equation [15].

Outcomes

The primary outcomes assessed were baseline patient characteristics (age, weight, gender, and presence of CKD). Secondary outcomes include rates and reasons for switching to DOAC, as well as those for switching back to warfarin from a DOAC. Reasons for switching from warfarin to DOAC therapy were abstracted from the medical chart when documented by the physician or anticoagulation clinic provider. These were categorized using pre-defined reasons. Not all patients had a documented reason for switching from warfarin to a DOAC medication.

Statistical analyses

Patient demographics and comorbidities were compared using Fisher's exact, Cochran-Armitage Trend Tests. A 2-sided test with $p < 0.05$ was considered statistically significant for all analyses. Analyses were performed using SAS version 9.3 (Cary, North Carolina, USA).

Results

Between 2010 to mid 2015, 400/3873 (10.3%) non-valvular AF patients switched from warfarin therapy to a DOAC. Of the patients who switched to a DOAC, 191 (47.8%)

switched to dabigatran, 130 (32.5%) to rivaroxaban, 75 (18.8%) to apixaban, and none to edoxaban. The percent of patient switching from warfarin to dabigatran declined during the study period while the percent of patients switching from warfarin to apixaban increased. Patients who switched to DOAC therapy were less likely to have advanced CKD or to take amiodarone compared to non-switchers. Overall, both groups were similar in baseline characteristics (age, weight, gender), risk scores (HAS-BLED and CHA_2DS_2-VASc), and insurance status (Table 1).

As shown in Table 2, warfarin treated AF patients more often switched to a DOAC for a patient related ease of use concern (37.5%) than a clinical reason (16.5%). The most common reasons for warfarin to DOAC switching was unstable INR (13.5%), challenges with access to blood drawing laboratories/need for frequent blood draws/need for any dose changes (9.8%), and concerns regarding patient adherence (4.3%).

Of the patients that switch to a DOAC, 52/400 (13%) switch back to warfarin. Roughly half of those patients (28/52, 53.8%) switched from a DOAC back to warfarin within the first 6 months of DOAC use. The most common reasons to switch from a DOAC back to warfarin were side effects (21.2%), clotting events (17.3%), and cost/insurance issues (13.5%) (Table 3).

Discussion

In our study of AF patients initiated on warfarin, 10% changed to DOAC therapy during the period of study. Of those who changed to a DOAC, 10% ended up switching back to warfarin for a variety of reasons. Surprisingly, the baseline characteristics between switchers and non-switchers are relatively similar. In fact, the presence of significant renal dysfunction was the only major difference between the two cohorts. This may be related to patient selection by prescribers given the renal clearance of the DOACs. Additionally, no difference was seen in bleeding and stroke risk or the insurance type. Finally, factors that contribute to patient ease of use and adherence had the greatest impact on the decision to switch from warfarin to a DOAC,

Table 1 Demographics and characteristics data

	Warfarin → DOAC switchers (at enrollment) N = 400 (10.3%)	Warfarin only (at enrollment) N = 3473 (88.0%)	p value
Demographics and comorbidities			
Age (mean ± SD)	69.8 ± 11.5	70.5 ± 12.7	0.32
Weight (mean ± SD)	202.7 ± 57.1	197.4 ± 70.6	0.19
Male	223 (55.8)	1965 (56.6)	0.75
Female	177 (44.3)	1508 (43.4)	
CKD stage III–V	82/303 (27.1)	1139/2812 (40.5)	<0.001
CrCl (mean ± SD)	72.7 ± 20.8	65.3 ± 24.7	<0.001
Labile INR (TTR <60%)	n/a	1831 (52.7) (entire study)	–
Risk scores (mean ± SD)			
CHA_2DS_2-VASc	3.4 ± 1.7	3.5 ± 1.8	0.42
HAS-BLED (without TTR)	2.6 ± 1.2	2.7 ± 1.3	0.14
Quality of warfarin usage			
Percent TTR	0.54 ± 0.22 (at switch)	0.55 ± 0.22 (entire study period)	–
Length of warfarin treatment (days)	389.3 ± 423.9 (at switch)	544.9 ± 559.8 (entire study period)	–
Insurance type			
Commercial insurance	83 (20.8)	697 (20.1)	0.75
Medicare	250 (62.5)	2038 (58.7)	0.14
Medicaid	5 (1.3)	66 (1.9)	0.44
Other (none/mixed)	62 (15.5)	672 (19.4)	0.06
Medications coadministered			
Amiodarone	32 (8.0)	415 (12.0)	0.02
Dronedarone	0	0	–
Verapamil	0	0	–
Aspirin	217 (54.3)	1811 (52.2)	0.42
P2Y12 inhibitor	29 (7.3)	247 (7.1)	0.92

SD standard deviation, *CKD* chronic kidney disease, *TTR* time in therapeutic range

Table 2 Warfarin to DOAC switcher data

Years of switch	2010–2011 N = 155 (%)	2012–2013 N = 125 (%)	2014–2015 N = 120 (%)	Total N = 400 (%)
DOAC agent switched to N (%)				
Dabigatran	153 (98.7)	30 (24.0)	8 (6.7)	191 (47.8)
Rivaroxaban	0	74 (59.2)	56 (46.7)	130 (32.5)
Apixaban	0	19 (15.2)	56 (46.7)	75 (18.8)
Other	2 (1.3)	2 (1.6)	0	4 (0.9)
Reason for switch				
Patient specific reasons (may answer more than one)	50 (32.2)	50 (40)	50 (41.6)	150 (37.5)
Unstable INR	14 (9.0)	23 (18.4)	17 (14.2)	54 (13.5)
Frequent blood draws/ dose changes/poor access to lab	18 (11.6)	9 (7.2)	12 (10.0)	39 (9.8)
Adherence concerns	4 (2.6)	7 (5.6)	6 (5.0)	17 (4.3)
Dietary restrictions	8 (5.2)	3 (2.4)	5 (4.2)	16 (4.0)
Warfarin side effects	3 (1.9)	4 (3.2)	5 (4.2)	12 (3.0)
Other	3 (1.9)	4 (3.2)	5 (4.2)	12 (3.0)
Clinical reasons (may answer more than one)	13 (8.4)	23 (18.4)	30 (25)	66 (16.5)
Bleeding event(s)	2 (1.3)	5 (4.0)	8 (6.7)	15 (3.8)
Superior alternative	2 (1.3)	6 (4.8)	5 (4.2)	13 (3.3)
Drug interactions	4 (2.6)	3 (2.4)	5 (4.2)	12 (3.0)
Clotting event	0	2 (1.6)	4 (3.3)	6 (1.5)
Other	5 (3.2)	7 (5.6)	8 (6.7)	20 (5.0)
Unknow reason for switch				238 (58.8)

DOAC direct oral anticoagulant, *INR* international normalized ratio

Clinical reason other: physician encouraged/PCP decision, prescribed by another physician, renal failure improved and hematoma secondary to Lovenox. Switched to apixaban upon hospital discharge

Patient preference reason other: patient or relatives request, patient interested in DOAC, patient and her husband are both switching to dabigatran, insurance company covers new agent or other Insurance related reason, patient didn't want to pay a $60 Quarterly fee for warfarin management, originally prescribed a DOAC, but on warfarin during insurance approval only

Table 3 DOAC to warfarin switch back data N (%)

Switch back to warfarin	52/400 (13.0)
Within 6 month	28 (7.0)
After 6 months	24 (6.0)
Reason for switch (N = 52)	
Side effects	11 (21.2)
Clotting event	9 (17.3)
Cost/insurance issue	7 (13.5)
Bleeding	6 (11.5)
Impaired renal function	3 (5.8)
Other	13 (25.0)
Unknown	5 (9.6)
Total (patients may have multiple reasons)	54 (104)

accounting for roughly two-thirds (150/216, 69%) of transitions for which data were collected.

Our study is unique as we examined not only the trends in anticoagulant use, but we also explored why the changes occurred. As with other studies of anticoagulant trends, we saw a rise in DOAC utilization during the year each respective DOAC became available, and overtime saw a relative drop in dabigatran use relative to the other DOACs [7, 16]. Also similar to other studies, we found that DOAC patients had better renal function relative to warfarin users, which is reassuring given that severe renal dysfunction is a contraindication for most DOAC medications [17]. However, several studies saw a difference in stroke and bleeding risk among DOAC patients, and others found DOAC users to be younger [6, 17, 18]. We did not find the differences in our population's risk scores for either bleeding or stroke, which may reflect the contrast between patients who were initially started on warfarin before switching to DOAC therapy (our study) vs. patients who start on DOAC therapy de novo (most other studies).

One other study claimed that patients are playing an increasingly collaborative role in prescribing habits, but that safety concerns, rather than compliance and lifestyle concerns were most important to patients [11]. Our real-world study appears to show rates of bleeding, stroke, and clotting events close to the expected findings of the original data, which is reassuring [1–3].

Our study design has multiple strengths. The study population is an inception cohort of newly initiated warfarin in AF patients, which reduces outside confounders such as prior experience using warfarin or a DOAC, or having failed an alternative treatment prior to the study. Trained abstractors who were familiar with the model of the anticoagulation clinics performed all the data collection and conducted random audits to validate the collected data. These factors ensure high quality retrospective data. The study is based on a unique cohort of patients, those having switched from warfarin to a DOAC, and who have not been well studied prior to this point.

Nevertheless, our study must be interpreted in the context of certain limitations. As it is an observational analysis, there are inherently potential confounders, and reduced generalizability of the study. However, our data registry has a heterogeneous patient population, including patients from rural and urban communities across Michigan. Also, the population covers several health systems, including private, public and academic institutions of various sizes. While the study predominately examined warfarin to DOAC transitions, the data regarding DOAC maintenance and transition back to warfarin may lack generalizability to current DOAC populations (predominately rivaroxaban and apixaban), as the majority of our patients initially switched to dabigatran, the first agent available, yet over the course of our study period, the relative new switches to dabigatran fell as the anti-Xa agents became available [6, 7]. Additionally, there were several patients whose reasons for switching from warfarin to a DOAC were unable to be collected. These unrecorded reasons may have skewed the data.

Conclusions

A significant population of AF patients elect to switch from warfarin to DOAC therapy for stroke prevention. While there are many factors at play in anticoagulant prescribing trends, patient preference factors are likely playing an increasing role. It remains to be seen how the introduction of DOAC-specific reversal agents will impact the clinical decision to remain on warfarin therapy or switch to DOAC therapy for stroke prevention in AF [19, 20].

Compliance with ethical standards

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883–891
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Aristotle Committees and Investigators (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
4. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, Engage, AF-TIMI 48 Investigators (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369:2093–2104
5. Barnes GD, Ageno W, Ansell J, Kaatz S, Subcommittee on the Control of Anticoagulation of the International Society on Thrombosis and Haemostasis (2015) Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost 13:1154–1156
6. Desai NR, Krumme AA, Schneeweiss S, Shrank WH, Brill G, Pezalla EJ, Spettell CM, Brennan TA, Matlin OS, Avorn J, Choudhry NK (2014) Patterns of initiation of oral anticoagulants in patients with atrial fibrillation-quality and cost implications. Am J Med 127(1075–82):e1
7. Weitz JI, Semchuk W, Turpie AG, Fisher WD, Kong C, Ciaccia A, Cairns JA (2015) Trends in prescribing oral anticoagulants in Canada, 2008–2014. Clin Ther 37(2506–2514):e4
8. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC (2012) National trends in oral anticoagulant use in the United States, 2007–2011. Circ Cardiovasc Qual Outcomes 5:615–621

9. Barnes GD, Lucas E, Alexander GC, Goldberger ZD (2015) National trends in ambulatory oral anticoagulant use. Am J Med 128(1300–5):e2

10. Steinberg BA, Holmes DN, Piccini JP, Ansell J, Chang P, Fonarow GC, Gersh B, Mahaffey KW, Kowey PR, Ezekowitz MD, Singer DE, Thomas L, Peterson ED, Hylek EM, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients (2013) Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. J Am Heart Assoc 2:e000535

11. Andrade JG, Krahn AD, Skanes AC, Purdham D, Ciaccia A, Connors S (2015) Values and preferences of physicians and patients with nonvalvular atrial fibrillation who receive oral anticoagulation therapy for stroke prevention. Can J Cardiol 32(6):747–753

12. Barnes GD, Kaatz S, Winfield J, Gu X, Haymart B, Kline-Rogers E, Kozlowski J, Beasley D, Almany S, Leyden T, Froehlich JB (2014) Warfarin use in atrial fibrillation patients at low risk for stroke: analysis of the Michigan anticoagulation quality improvement initiative MAQI^2. J Thromb Thrombolysis 37:171–176

13. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY (2010) 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 138:1093–1100

14. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E (1993) A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 69:236–239

15. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41

16. Adelborg K, Grove EL, Sundboll J, Laursen M, Schmidt M (2016) Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. Heart. doi:10.1136/heartjnl-2016-309402

17. Baker D, Wilsmore B, Narasimhan S (2016) Adoption of direct oral anticoagulants for stroke prevention in atrial fibrillation. Intern Med J 46:792–797

18. Hanemaaijer S, Sodihardjo F, Horikx A, Wensing M, De Smet PA, Bouvy ML, Teichert M (2015) Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands. Int J Clin Pharm 37:1128–1135

19. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI (2015) Idarucizumab for dabigatran reversal. N Engl J Med 373:511–520

20. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Sinha U (2013) A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med 19:446–451