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BRIEF REPORT

Reasons for discontinuation of novel oral anticoagulant therapy in patients with atrial fibrillation

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ABSTRACT

Aims: We sought to investigate the reasons for, and rates of, novel oral anticoagulant (DOAC) therapy discontinuation.

Methods: This was an observational cohort study of patients with atrial fibrillation (AF) referred to a regional DOAC outpatient clinic between February 2013 and October 2017. The study population consisted of 875 consecutive patients with AF who visited the DOAC outpatient unit to initiate treatment with apixaban ($N=303$), dabigatran ($N=267$) or rivaroxaban ($N=305$) for long-term ischemic stroke prophylaxis. All the patients came from the Leeuwarden Medical Center cardiology outpatient clinic, which offers a well structured and nurse-run DOAC unit in cooperation with the hospital's thrombosis service. This clinic operates according to the Dutch nationwide guidelines on integration of anticoagulation services.

Results: Overall rate of discontinuation was 11.9 per 100 patient-years of follow-up. Discontinuation rates for apixaban, dabigatran and rivaroxaban were 8.1, 16.6 and 11.5 per 100 patient-years of follow-up.

Apixaban had the lowest rate of discontinuation during the 36 month follow-up period. Dabigatran and rivaroxaban had high discontinuation rates during the 3–6 month period following DOAC therapy initiation. The main reasons for discontinuation of DOAC therapy were adverse side effects, patient-initiated discontinuation and any bleed.

Limitation: This was a retrospective and non-randomized study, and our results should be interpreted in light of these observations.

Conclusion: DOAC discontinuation rates varied significantly and appeared related to drug-specific side effects, patient-initiated discontinuation and bleeding. We observed longer-term administration of apixaban, suggesting that this drug is better tolerated than dabigatran or rivaroxaban.

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DOAC; anticoagulation; apixaban; rivaroxaban; dabigatran

Introduction

Novel oral anticoagulation drugs (DOAC medications) entered the market in the Netherlands beginning in 2009. Non-vitamin-K oral anticoagulants such as apixaban, dabigatran, edoxaban and rivaroxaban are direct selective inhibitors of activated coagulation factors X or II. DOAC medications have a good dose–response relationship that eliminates the need to closely control coagulation levels. DOACs are less likely to interact with other medications compared to vitamin K antagonists. Several studies have confirmed the superior or similar efficacy and safety of DOAC medications over vitamin K antagonist (VKA) drugs with respect to stroke and systemic embolic events (SEEs), ischemic stroke, cerebral hemorrhage, all-cause mortality, myocardial infarction and major, intracranial or gastrointestinal bleeding^{1–5}.

In 2017, nearly 575,000 people in the Netherlands were treated with VKAs or DOACs⁶. Approximately 115,000 were first-time users. Since 2016 there has been a decline in the number of VKA prescriptions as more and more patients

initiate therapy with, or transition to, DOAC medications. In 2017, there were more DOAC (62,500) than VKA (52,500) prescriptions issued to first time users⁶. The percentage of DOAC medications prescribed, relative to the total number of anticoagulant Defined Daily Doses (DDD) that were prescribed, grew from 18% in 2015 to 44% in 2017. Given that more and more people are taking DOAC medications, we must understand how patients experience this class of drugs in real life. Approximately 20% of patients who take DOAC medications discontinue therapy prematurely, typically within 6–12 months^{7–15}. Less is known about the reasons for why patients continue to take, or discontinue, these drugs in “real life” settings. These data could help us understand how patients comply with DOACs when they are not intensively monitored, as they are with VKA.

The central aim of this study was to investigate the reasons why patients discontinue DOAC therapy. We also evaluated risk factors for discontinuation, and rates of discontinuation in Dutch patients with AF.

Methods

Study population

All the patients (consecutive and unselected) were recruited for participation from the Leeuwarden Medical Center cardiology outpatient clinic. This clinic features a well structured and nurse-based DOAC unit that operates in cooperation with hospital's thrombosis service. This clinic operates in accordance with Dutch guidelines governing integrated anticoagulation services¹⁶. These guidelines describe how DOACs should be prescribed and administered. According to these guidelines, the prescribing cardiologist and thrombosis nurse are responsible for initiating DOAC therapy, informing patients of the risks and benefits of DOAC therapy, therapy follow-up consultations, patient monitoring and information transfers to other healthcare providers included in the guidelines.

At our DOAC clinic, thrombosis service nurses initiate DOAC treatment in patients with AF who were previously diagnosed by a referring cardiologist. Using a checklist, thrombosis service nurses review the treatment indications, prescribed dose, presence of comorbidities, patient's renal function, and risk of thrombosis or bleeding as per CHA₂DS₂-VASc and HAS-BLED scores. They also provide the patients with relevant information about DOAC medications. Patients are routinely scheduled for 3, 6 and 12 month follow-up appointments. At these appointments, the nurses will carefully monitor and document patients' renal function and experiences with DOAC therapy. After the initial 12 months of DOAC therapy, patients are scheduled for once yearly follow-ups.

The patients are also encouraged to contact the nurses if they experience adverse side effects (including bleeding) or participate in planned interventions that might necessitate temporary DOAC medication discontinuation. The nurses used standardized question lists for side effects at each clinic visit. These observations are subsequently documented in the patient's electronic medical record. The dose and type of DOAC may be changed during follow-up visits due to deteriorations in renal function, age, bleeding risk, medication side effects or the patient's wishes after conferring with the referring cardiologist. Because of the clinic's well structured follow-up processes, we were able to collect high quality and detailed data on patients who were administered DOAC medications. Atrial fibrillation patients who previously were treated with VKAs were included.

Exclusion criteria

Exclusion criteria were as follows:

- Patients with persistent AF who required temporary DOAC therapy for scheduled cardioversion or pulmonary vein isolation were excluded.
- Patients using DOAC for off label indication (like stroke prevention in prosthetic or mechanical heart valves) were excluded.
- Atrial fibrillation patients who during the study switched to another DOAC were not enrolled multiple times.

Study design

This was an observational population based cohort study of patients with AF who were referred to the single DOAC outpatient clinic between February 2013 and October 2017. All patients with indications for DOACs for AF were included in the study.

All clinical data generated during the course of usual care were prospectively collected using the patients' electronic medical records. This EMR system (EPD vision) collects and stores patient DOAC treatment data and records contacts with other health providers for DOAC-related problems, side effects, bleeding episodes, cardiovascular events, cerebrovascular events, medication changes or discontinuations, and deaths. Patients were followed up for a maximum of 3 years.

Definitions of variables

The primary outcome measure was time to discontinuation of DOAC therapy. Discontinuation refers exclusively to complete stop of medication or switch to another (D)OAC during the follow up. Time to discontinuation was defined as the time from DOAC medication initiation until discontinuation. Secondary objectives were the reasons for discontinuation (side-effects, bleeding, patient-initiated discontinuation or various medical conditions) and risk factors for DOAC therapy discontinuation (age, gender, renal function, CHA₂DS₂-VASc and HAS-BLED scores, blood pressure, and prior VKA therapy).

Ethics

The researchers were granted a waiver of informed consent by the regional ethical committee, in accordance with Dutch laws.

Statistics

Variables are presented as mean $\pm$ standard deviation if normally distributed, and median and range if non-normally distributed. Categorical variables are presented using frequency counts and percentages.

Between-group differences in baseline characteristics were tested using the chi square test for categorical variables and ANOVA or Kruskal–Wallis procedures for continuous variables, depending on the data distribution. The time to DOAC discontinuation was depicted graphically using the Kaplan–Meier approach. Associations between discontinuation and the patients' characteristics were tested using univariate and multivariable Cox proportional hazard regression analyses. In cases where indications for DOACs were no longer present patients were censored (e.g. cancer, watchman procedure).

Results

Study population

The study population consisted of 875 consecutive patients with AF who visited the DOAC outpatient unit for initiation of treatment with apixaban ($N=303$), dabigatran ($N=267$) or rivaroxaban ($N=305$) for long-term ischemic stroke

prophylaxis (Table 1). Median follow-up time was 15.7 months for the whole cohort (95% CI 14.9–16.6), 14.5 months (95% CI 13.8–15.9) for apixaban, 15.0 months (95% CI 14.0–17.0) for dabigatran and 18.2 months (95% CI 16.2–23.7) for rivaroxaban. The median age was 70 years (range 39–98) and females accounted for 36% of the total study population. Most of the patients had received prior VKA therapy (52%) ($N=455$). Out of the 875 patients, 74 stopped due to an unplanned event

that resulted in a lack of indication for DOAC treatment. Of these, 23 were administered apixaban, 31 were administered dabigatran and 20 were administered rivaroxaban.

Discontinuation of DOAC medications

Figure 1 presents the Kaplan–Meier estimate for drug discontinuation (survival), stratified by DOAC. Overall rate of

Table 1. Baseline characteristics.

Variable	Apixaban $N=303$	Dabigatran $N=267$	Rivaroxaban $N=305$	Total $N=875$	p value
Age	72 ± 9	69 ± 9	69 ± 9	70 ± 9	<.001
Male	184 (61)	174 (65)	201 (66)	559 (64)	.36
Female	119 (39)	93 (35)	104 (34)	316 (36)	
eGFR mL/min at start	75 (63–87)	76 (65–86)	72 (63–82)	74 (63–85)	.022
Diastolic blood pressure	84 ± 12	85 ± 12	83 ± 10	84 ± 11	.16
Systolic blood pressure	142 ± 19	143 ± 20	140 ± 18	142 ± 19	.17
HAS-BLED score					
0	38 (13)	46 (17)	42 (14)	126 (14)	.14
1	124 (41)	118 (44)	130 (43)	372 (43)	
2	94 (31)	83 (31)	103 (34)	280 (32)	
3	34 (11)	17 (6)	23 (8)	74 (9)	
4	11 (4)	3 (1)	5 (2)	19 (2)	
Unknown	2	0	2	4	
CHA ₂ DS ₂ -VASc score					
0–1	55 (18)	65 (24)	58 (19)	178 (20)	.026
2	75 (25)	84 (32)	97 (32)	256 (29)	
3	67 (22)	56 (21)	78 (26)	201 (23)	
4	59 (20)	34 (13)	42 (14)	135 (16)	
>4	46 (15)	28 (10)	29 (9)	103 (12)	
Unknown	1	0	1	2	
Prior VKA therapy					
No	153 (51)	123 (46)	144 (47)	420 (48)	.54
Yes	150 (49)	144 (54)	161 (53)	455 (52)	
Reduced dose of DOAC	57 (19)	68 (26)	42 (14)	167 (19)	.002
Reasons for starting DOAC therapy					
Advice of cardiologist	64 (41)	48 (33)	54 (34)	166 (36)	.016
Advice of general practitioner	0 (0)	2 (1)	2 (1)	4 (1)	
Advice of thrombosis service	1 (1)	1 (1)	0 (0)	2 (0.4)	
Advice of neurologist	5 (3)	5 (3)	0 (0)	10 (2)	
Unstable INR	15 (10)	13 (9)	10 (6)	38 (8)	
No INR control needed	47 (30)	59 (40)	79 (49)	185 (40)	
Side effects of VKA	13 (8)	8 (5)	3 (2)	24 (5)	
Bleeding with VKA	9 (6)	6 (4)	4 (2)	19 (4)	
Other	3 (2)	4 (3)	9 (6)	16 (3)	

Categorical variables are presented as N (%), continuous variables are presented as mean $\pm$ SD or median (Q1–Q3), and analyzed with ANOVA or Kruskal–Wallis tests, as appropriate. The p values (test for independence between DOAC medications and the respective baseline variable) tested the null hypothesis of no differences among the three types of DOAC medications.

Abbreviations. eGFR, estimated Glomerular Filtration Rate; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; INR, international normalized ratio.

Figure 1. Kaplan–Meier curve for DOAC discontinuation events for apixaban, dabigatran and rivaroxaban.

discontinuation was 11.9 (95%; 10.0–14.1) per 100 patient-years of follow-up. Discontinuation rates for apixaban, dabigatran and rivaroxaban were 8.1 (95% CI 5.5–11.6), 16.6 (95% CI 12.5–21.5) and 11.5 (95% CI 8.6–15.1) per 100 patient-years of follow-up. Time to discontinuation was median months (q1–q3) 3.5 months (0.95–5.5) for apixaban ($N=30$), 3.8 months (2.4–8.1) for dabigatran ($N=56$) and 3.3 months (0.9–10.5) for rivaroxaban ($N=52$).

Our data show that dabigatran was associated with more instances of drug discontinuations, compared to rivaroxaban or apixaban. Apixaban had the fewest instances of drug discontinuations over the whole follow-up period. The highest rate of drug discontinuation for dabigatran and rivaroxaban

occurred during the first 3–6 months following DOAC initiation (8–13%). The most frequently cited reasons for DOAC discontinuation were side effects, followed up by patient-initiated discontinuation and bleeding (Table 2).

When considering drug discontinuation specifically related to adverse events (side effects and bleeding) we found that apixaban still has a lower chance of discontinuation compared to dabigatran (adjusted HR 1.9; 95% CI 1.1–3.2) and rivaroxaban (adjusted HR 1.9; 95% CI 1.1–3.2). In this case there is no difference between dabigatran and rivaroxaban.

Reported side effects of DOACs

Reported side effects of each DOAC medication are listed in Table 3. There were significant differences in reported side effects for the various DOAC medications. Our data showed that patients who received rivaroxaban reported the most side effects, 51% ($n=157$ out of 318, p value $<.001$). Rivaroxaban users experienced significantly more side effects that involved nervous (dizziness, headache), integumentary disturbances (itching) and circulatory system disorders (edema). Dabigatran users experienced significantly more side effects that related to the digestive system, including dyspepsia and diarrhea.

Our univariate Cox regression analysis results indicated that only the type of DOAC was significantly associated with discontinuation (dabigatran HR 2.14, 95% CI [1.37–3.33], $p=.0008$ and rivaroxaban HR 1.63, 95% CI [1.04–2.55], $p=.00347$ versus apixaban) (Table 4 and Figure 2). On the multivariable model

Table 2. Reasons for DOAC discontinuation.

Variable N (%)	Apixaban $N=303$	Dabigatran $N=267$	Rivaroxaban $N=305$
Discontinued patients	30 (9.9)	56 (21)	52 (17.0)
Reasons for discontinuation, n (% of discontinuation)			
Side effects	19 (63)	33 (59)	38 (73)
Bleeding	5 (17)	5 (9)	7 (13)
Patient decision	3 (10)	11 (20)	5 (10)
Various medical conditions*	3 (10)	7 (13)	2 (4)
Outcome of DOAC discontinuation (% of discontinuation)			
Change to other DOAC	27	43	50
Change to VKA	57	32	44
Change to antiplatelet therapy	10	11	0
Change to LMWH	0	2	2
Withdrawal of anticoagulation therapy	7	13	4

*Various medical conditions which resulted in DOAC discontinuation, as determined by a physician, worsened renal function, new or recurrent stroke.

Abbreviations. VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparine.

Table 3. Reported side effects.

Side effect	Apixaban $N=303$	Dabigatran $N=267$	Rivaroxaban $N=305$	Total $N=875$	p value
Total	56 (19%)	105 (39%)	157 (51%)	318 (36%)	$<.001$
Nervous system					
Dizziness	11 (4%)	8 (3%)	69 (23%)	88 (10%)	$<.001$
Nausea	8 (3%)	10 (4%)	13 (4%)	31 (4%)	.53
Headache	10 (3%)	5 (2%)	37 (12%)	52 (6%)	$<.001$
Pain	4 (1%)	1 (0.4%)	2 (1%)	7 (1%)	.46
Loss of consciousness	0 (0%)	1 (0.4%)	6 (2%)	7 (1%)	.017
Tiredness	4 (1%)	2 (1%)	12 (4%)	18 (2%)	.013
Tinnitus	1 (0.3%)	2 (1%)	2 (1%)	5 (1%)	.87
Tingling	2 (1%)	0 (0%)	2 (1%)	4 (0.5%)	.56
Digestive system					
Diarrhea	5 (2%)	25 (9%)	12 (4%)	42 (5%)	$<.001$
Obstipation	2 (1%)	1 (0.5%)	15 (5%)	18 (2%)	$<.001$
Vomiting	1 (0.5%)	0 (0%)	0 (0%)	1 (0.1%)	.65
Dyspepsia	3 (1%)	41 (15%)	5 (2%)	49 (6%)	$<.001$
Dry mouth	0 (0%)	1 (0.5%)	2 (1%)	3 (0.5%)	.53
Integumentary system					
Itching	6 (2%)	3 (1%)	36 (12%)	45 (5%)	$<.001$
Rash	0 (0%)	0 (0%)	7 (2%)	7 (1%)	$<.001$
Hair loss	0 (0%)	1 (0.5%)	0 (0%)	1 (0.1%)	.31
Circulatory system					
Edema	2 (1%)	1 (0.5%)	27 (9%)	20 (3%)	$<.001$
Hypotension	1 (0.5%)	0 (0%)	4 (1%)	5 (1%)	.14
Increased heart rate	3 (1%)	3 (1%)	8 (3%)	14 (2%)	.23
Pulmonary system					
Dyspnea	3 (1%)	2 (1%)	7 (2%)	12 (1%)	.24
Musculoskeletal system					
Muscle pain	3 (1%)	3 (1%)	6 (2%)	12 (1%)	.58
Joint pain	2 (1%)	0 (0%)	1 (0.3%)	3 (0.3%)	.65
Reproductive system					
Erectile dysfunction	0 (0%)	2 (1%)	0 (0%)	2 (0.2%)	.093
Diverse					
Elevated liver enzymes	4 (1%)	3 (1%)	5 (2%)	12 (1%)	.94
Fever	0 (0%)	0 (0%)	1 (0.3%)	1 (0.1%)	1.00

Table 4. Univariate association between discontinuation and patient characteristics.

	Hazard ratio (95% CI), <i>p</i> value	Overall <i>p</i> value
Type of DOAC		.004
Dabigatran vs. apixaban	2.14 (1.37–3.33), .0008	
Rivaroxaban vs. apixaban	1.63 (1.04–2.55), .0347	
Dabigatran vs. rivaroxaban	1.31 (0.90–1.92), .157	
Age (years)		.40
Age 65–75 vs. <65	1.31 (0.84–2.03), .2310	
Age >75 vs. <65	1.36 (0.84–2.20), .2077	
Gender		.179
Males vs. female	1.26 (0.90–1.77)	
Renal function		.140
eGFR >50 vs. <50	1.71 (0.84–3.50)	
HAS-BLED		.18
HAS-BLED 1 vs. 0	1.71 (0.90–3.26), .1002	
HAS-BLED >1 vs. 0	1.40 (0.63–3.12), .0661	
CHA ₂ DS ₂ -VASc		.28
CHA ₂ DS ₂ -VASc 2 vs. ≤1	0.94 (0.56–1.57), .7991	
CHA ₂ DS ₂ -VASc 3 vs. ≤1	1.44 (0.87–2.38), .1563	
CHA ₂ DS ₂ -VASc 4 vs. ≤1	0.92 (0.50–1.70), .7945	
CHA ₂ DS ₂ -VASc ≥4 vs. ≤1	1.25 (0.68–2.31), .4271	
Prior VKA therapy		.089
Prior VKA therapy vs. VKA naive	1.34 (0.96–1.87)	
Prior bleeding		.61
Prior bleeding under VKA therapy vs. no bleeding	1.13 (0.71–1.80)	
Reduced dose of DOAC vs. standard dose	1.05 (0.7–1.58)	.82

Abbreviations. DOAC, direct oral anticoagulant; eGFR, estimated Glomerular Filtration Rate; VKA, vitamin K antagonist.

Figure 2. Univariate and multivariate model.**Table 5.** Multivariable model.

	Hazard ratio (95% CI)	<i>p</i> value (< .05)
Prior VKA therapy	0.74 (0.53–1.03)	.075
Dabigatran treatment	2.16 (1.38–3.36)	.0007
Rivaroxaban treatment	1.63 (1.04–2.56)	.0326

Associations between discontinuation outcomes and different patient characteristics were tested with multivariable Cox proportional hazard regression analysis ($p < .05$).

(Table 5 and Figure 2), only dabigatran and rivaroxaban were significantly associated with DOAC discontinuation.

Discussion

Our data detail the treatment durations and side effects associated with three different DOAC medications (apixaban, dabigatran and rivaroxaban) following initiation and long-term follow-up within our DOAC clinical unit. This is one of the few long-term population-based follow-up studies to

compare multiple DOAC medications administered through a DOAC specialty clinic.

Our clinical practice data showed variable tolerability and treatment duration for three DOAC medications. Further, DOAC side effects and rates of discontinuation varied significantly among the various varieties of DOAC medication. Dabigatran had the highest discontinuation rate. This was attributable to drug-related side effects, the most common of which was dyspepsia. Rivaroxaban was associated with the most side effects, most of which involved the nervous system. Apixaban had the lowest discontinuation rate and significantly fewer reported side effects. When considering drug discontinuation specifically related to adverse events we found that apixaban still has a lower chance of discontinuation compared to dabigatran and rivaroxaban.

Most patients discontinued DOAC therapy because of side effects (65% of all discontinuations), followed by patient-initiated discontinuation (14%) and bleeding (12%).

In past DOAC clinical trials, discontinuation rates generally ranged from 21% to 25% (follow-up 12–24 months), and patient-initiated discontinuation accounted for 8–10% of all discontinuations within the treated population^{7,13}. In our study, relatively few patients (2%, $n = 19$) discontinued DOAC therapy on their own. This could be attributable to the structured care patients received within the specialty DOAC clinic. The highest rate of patient initiation was in the dabigatran group. This could have been affected by negative publicity about the drug that was generated in the media shortly after the introduction of this novel therapy. We compared our dabigatran discontinuation rates during follow-up (21%, of which 59% were attributable to side effects and 9% to bleeding) to the published findings of Al Khalili et al.¹³ (30%, $n = 70$ of which 63% were attributable to side effects and 17% to bleeding) and the Dresden Dabigatran Registry (25.8%, of which 32% were attributable to side effects and 8% to bleeding). Additional side effects could have been realized during the longer follow-up period of our study, in comparison to large studies. A recent international, prospective and observational study of rivaroxaban showed a 20.1% discontinuation rate at 1 year which is slightly higher than our results¹⁷.

In Norway, from 2013 to 2015, 20% of dabigatran users, 16% of warfarin users, 12% of rivaroxaban users, and 6% of apixaban users switched to another oral anticoagulant within 12 months of the first dispensing¹¹. A Danish study reported similar rates of transition within 1 year (17% for dabigatran, 14% for rivaroxaban and 8% for apixaban)¹¹. In a UK cohort study of primary care patients with AF non-compliance rates were higher with dabigatran (HR 1.67 [1.20–2.32]) and rivaroxaban (HR 1.41 [1.02–1.93]) than apixaban. There were no differences in patient compliance between VKA and apixaban (HR 0.92 [95% CI 0.68–1.23])⁹. In this study, patients discontinued VKA mainly due to bleeding and the reasons for DOAC discontinuation were unreported. The highest rates of non-compliance were measured within 2 months after initiation of therapy⁹. In the Dresden DOAC registry trial, patients who were prescribed warfarin tended to discontinue therapy because of unstable international normalized ratios (INRs) and bleeding-related complications. In contrast, rivaroxaban and dabigatran users discontinued DOAC treatment because of non-hemorrhagic side effects, bleeding-related complications, unstable sinus rhythm and worsening renal function. Thromboembolic complications rarely induced treatment changes¹⁸.

In our study, most patients who discontinued DOAC therapy transitioned to another oral anticoagulant (Table 2). Most patients started DOAC therapy because of poor INR control and on the recommendation of their cardiologists.

Patients treated with apixaban were significantly older. This could be caused by the fact that apixaban is considered a “safer” alternative in older patients because of its low associated bleeding risk. Overall, long-term drug compliance for DOAC medications is good when compared to other drugs.

This study had several limitations. Our data were collected retrospectively and our cohort was non-randomized. One strength of this study was our relatively long study duration

period of 36 months compared to other studies. We also examined a large group of patients and obtained detailed follow-up records. We have prospectively collected data on patients who used VKA therapy prior to DOAC therapy and determined their reasons for switching. Side effects were reported using standard side effect questionnaires, administered by specialty nurses. In the country of research (The Netherlands) patient access, insurance or costs are no issue with adherence.

Conclusion

In our DOAC outpatient clinic, rates of discontinuation varied significantly among different DOAC medications. Discontinuations were attributable to drug-specific side effects, patient-initiated discontinuation and bleeding. Apart from the type of DOAC, no other factors predicted DOAC discontinuation. Compared to apixaban, use of dabigatran and rivaroxaban was associated with a higher risk of discontinuation by 3–6 months following initiation of drug therapy.

Transparency

Declaration of funding

There is no funding to disclose.

Author contributions

D.M. and R.F. gathered data; D.M. and E.v.R. initiated and designed research; N.V. performed statistical analysis; D.M. and E.v.R. analyzed results; and D.M., R.F., N.V. and E.v.R. contributed to writing this article or reviewed this article.

Declaration of financial/other relationships

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