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Equivalent thrombotic risk with Warfarin, Dabigatran, or Enoxaparin after failure of initial direct oral anticoagulation (DOAC) therapy

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Abstract

Background The direct oral anticoagulants (DOACs) are now commonly regarded as first line anticoagulants in most cases of venous thromboembolism (VTE). However, the optimal choice of subsequent anticoagulant in instances of first line DOAC failure is unclear.

Objectives To describe and compare outcomes with second line anticoagulants used after DOAC failure.

Methods Patients seen at an urban hospital system for an episode of acute VTE initially treated with either apixaban or rivaroxaban who experienced a subsequent recurrent thrombosis while on anticoagulation (1st recurrent thrombosis) were included.

Results In total, 166 patients after apixaban or rivaroxaban failure were included. Following DOAC failure (1st recurrent thrombosis), the subsequent anticoagulant was warfarin in 60 patients (36%), dabigatran in 42 patients (25%), and enoxaparin in 64 patients (39%). Enoxaparin was preferentially prescribed in patients with a malignancy-associated etiology for 1st recurrent thrombosis ($p < 0.01$). The median follow-up time in our cohort was 16 months. There was no difference in 2nd recurrent thrombosis-free survival ($p = 0.72$) or risk for major bleeding event ($p = 0.30$) among patients treated with dabigatran, warfarin, or enoxaparin.

Conclusions In this retrospective analysis of patients failing first line DOAC therapy, rates of 2nd recurrent thrombosis and bleeding did not differ among subsequently chosen anticoagulants. Our study provides evidence that the optimal 2nd anticoagulant is not clear, and the choice of 2nd anticoagulant should continue to balance patient preference, cost, and provider experience.

Essentials

- Little is known about subsequent anticoagulation selection when DOACs fail.
- We compared warfarin, enoxaparin, and dabigatran usage outcomes in the setting of DOAC failure.
- 2nd recurrent thrombosis and bleeding risk did not differ significantly.
- Choice of 2nd anticoagulant should consider history, cost, administration, and monitoring.
- Prospective multicenter studies are needed to explore anticoagulation choices after DOAC failure.

Keywords Anticoagulants · Direct acting oral anticoagulants · Treatment failure · Venous thromboembolism · Venous thrombosis · Warfarin

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Introduction

The direct oral anticoagulants (DOACs) apixaban and rivaroxaban are increasingly prescribed due to convenient oral formulation without the need for routine laboratory monitoring. They are now commonly regarded as first line anticoagulants in most cases of venous thromboembolism (VTE) [1]. However, the optimal choice of subsequent anticoagulant in instances of first line DOAC failure is unclear.

Apixaban and rivaroxaban are highly effective in treating VTE and have low failure rates. From the landmark trials that led to their approval, the occurrence of recurrent thromboembolism or treatment failure of these DOACs was 2–3% [2, 3]. Subsequent studies confirmed low DOAC failure rates, with a meta-analysis demonstrating an event rate of 1.08 per 100 person-years for patients with VTE being treated with extended anticoagulation [4]. In patients with inherited thrombophilia (i.e., factor V Leiden; prothrombin gene mutation; protein C, protein S and antithrombin deficiencies), treatment failure with DOACs is 1.9% and similar to those without known thrombophilia [5]. For patients with cancer, there is a 3-fold risk of recurrent VTE when compared to patients without cancer [6]. The pivotal noninferiority trials comparing DOACs to low molecular weight heparin (i.e., enoxaparin) demonstrated recurrent thromboembolic rates of 4% with rivaroxaban and 5.6% with apixaban in cancer patients [7, 8]. DOAC failure is low, however the risk is not negligible, and the optimal subsequent treatment strategy is unknown.

There is limited data on the outcomes and management after recurrent VTE while on anticoagulation. Schulman et al. described the outcomes of 212 cancer patients with breakthrough thromboembolic events while on anticoagulation [6]. This study was done before the approval of DOACs in cancer patients, so the cohort was only treated with warfarin or enoxaparin. Despite the increased use of DOACs over the past decade, to our knowledge, there has only been one study describing the management strategies after DOAC failure [9]. A retrospective study by McIlroy et al. included 54 patients with a breakthrough VTE while on a DOAC, 57% of whom were on apixaban 5 mg twice daily (BID) and 28% of whom were on rivaroxaban 20 mg daily. At the time of recurrent VTE, most patients were temporarily treated with enoxaparin, and then subsequently switched back to an oral anticoagulant, typically another DOAC. Additional recurrent VTE events were not evaluated and thus, it is unknown what the efficacy of these subsequent anticoagulation strategies are.

Due to this paucity of data on subsequent treatment strategies, there are currently no established guidelines for the management of DOAC failure. If a breakthrough event occurs while on therapeutic anticoagulation, it may be reasonable to consider switching to another anticoagulant with a different route of administration like enoxaparin or a separate mechanism of action such as warfarin or dabigatran to reduce the risk of further thrombotic events.

Recurrent thromboses while on DOACs are rare but present a challenging situation as the optimal next line therapy is unknown. There is currently no literature on clinical outcomes after DOAC failure. In this study, we compared the recurrent VTE rates and bleeding risk of second line anticoagulant therapies (warfarin, enoxaparin, dabigatran) to identify an optimal treatment strategy after rivaroxaban or apixaban treatment failure.

Methods

Adult patients who had a VTE episode treated with either apixaban or rivaroxaban and had a subsequent thrombosis episode (1st recurrent thrombosis) while on a DOAC and who were subsequently treated with warfarin, dabigatran, or enoxaparin between January 1 2010 and September 1 2022 were identified in our urban hospital system's electronic medical record. Patients on DOAC therapy for less than two weeks or who had antiphospholipid syndrome were excluded.

Information on the cause and location of initial and 1st recurrent thrombus, 2nd anticoagulation choice and duration, and reason for stopping 2nd anticoagulation were collected. Locations were described as one of the following: pulmonary embolism (PE), extremity deep vein thrombosis (DVT), other VTE (i.e., splanchnic, cerebral vein), or arterial thrombus. The following outcomes data were also recorded: occurrence of major bleeding, 2nd recurrent thrombosis despite change in anticoagulation, and death from any cause. Major bleeding was defined as a decrease in hemoglobin level of 2 g/dL or more, bleeding that required blood transfusions of two or more units of blood, bleeding into a critical site (i.e., intracranial, retroperitoneal), or bleeding that contributed to death following guidelines by the International Society on Thrombosis and Haemostasis [10]. Relevant comorbid conditions recorded included active cancer, thrombophilia, and inflammatory bowel disease. Each chart was independently assessed by one of four reviewers for eligibility with at least 20% of each reviewer's coding examined by another reviewer for concordance.

Statistical analysis

Continuous patient-related, disease-related, and treatment-related variables were summarized by the median and interquartile range (IQR), while categorical variables were summarized by N (%). Distributions of continuous and

categorical variables were compared using analysis of variance (ANOVA) and chi-square test, respectively.

The primary outcome (2nd recurrent vascular event) was assessed using the Kaplan-Meier method (which was used to compare time-to-event distributions among the three treatment groups). All patients who did not have a 2nd recurrent vascular event were censored at last follow-up. Comparisons of time to event distributions between groups were made using the log-rank test.

Multivariable Cox-proportional hazards modeling was performed to estimate adjusted hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs). The variables included and adjusted for in the multivariable model were anticoagulant used (enoxaparin, dabigatran, warfarin), etiology of 1st recurrent thrombosis (malignancy, other provoked, unprovoked), and site of 1st recurrent thrombosis (PE, extremity DVT, other VTE, arterial).

Results

A total of 173 patients met the eligibility criteria. Six patients were then excluded for lack of follow-up data after the 1st recurrent thrombosis and one was excluded for not taking the DOAC at the time of recurrence leaving 166 patients in the final analysis (Table 1).

In the total cohort, 51% had failed apixaban and 49% had failed rivaroxaban. The median time on a DOAC prior to a recurrent VTE event was 149 days or roughly 5 months. Regarding the thrombotic events that occurred while on a DOAC, 57% were extremity DVT, 23% were PE, 10% were other VTE, and 10% were arterial thrombus. Of the thrombotic events, 28% were malignancy-related, 30% were provoked (non-malignancy related), and 42% were unprovoked.

Following apixaban or rivaroxaban failure (1st recurrent thrombosis), the subsequently prescribed anticoagulant was warfarin in 60 patients (36%), dabigatran in 42 patients (25%), and enoxaparin in 64 patients (39%). There was no significant difference in location of 1st recurrent thrombosis ($p = 0.93$). Patients with a malignancy related thrombus for their 1st recurrent thrombosis were more likely to be treated with enoxaparin (48%) as opposed to dabigatran (21%) or warfarin (12%) ($p < 0.01$).

The median follow-up interval in our group of patients was 16 months (IQR 4–34 months). Recurrent thrombosis while on warfarin, dabigatran, or enoxaparin (2nd recurrence) occurred in 27 of 166 patients (16.3%). As shown in Fig. 1, there was no statistically significant difference in 2nd

Table 1 Baseline characteristics of patients with recurrent thrombotic events when initially treated with apixaban or rivaroxaban

	All	Dabigatran	Enoxaparin	Warfarin	*p*-value
n	166	42	64	60	
Age, years, median (IQR)	62 (48–71)	60 (45–69)	62 (50–71)	63 (50–73)	0.42
Male sex, n (%)	80 (48)	25 (60)	25 (39)	30 (50)	0.11
BMI, median (IQR)	29 (25–33)	27 (24–31)	29 (25–32)	31 (26–35)	0.20
Race, n (%)					
Black	57 (34)	17 (40)	20 (31)	20 (33)	0.76
Hispanic	40 (24)	7 (17)	19 (30)	14 (23)	
White	59 (36)	16 (38)	22 (34)	21 (35)	
Other	10 (6)	2 (5)	3 (5)	5 (8)	
Initial anticoagulation, n (%)					
Apixaban	85 (51)	27 (64)	31 (48)	27 (45)	0.14
Rivaroxaban	81 (49)	15 (36)	33 (52)	33 (55)	
Etiology of recurrent thrombosis, n (%)					
Malignancy	47 (28)	9 (21)	31 (48)	7 (12)	< 0.00
Other provoked	49 (30)	12 (29)	21 (33)	16 (27)	
Unprovoked	70 (42)	21 (50)	12 (19)	37 (62)	
Location of recurrent thrombosis, n (%)					
PE	38 (23)	8 (19)	16 (25)	14 (23)	0.93
Extremity DVT[a]	95 (57)	25 (60)	35 (55)	35 (58)	
Other VTE[b]	17 (10)	6 (14)	6 (9)	5 (8)	
Arterial thrombosis[c]	16 (10)	3 (7)	7 (11)	6 (10)	
Follow-up, months, median (IQR)	16 (4–34)	17 (7–34)	12 (2–25)	22 (6–47)	0.02

IQR, interquartile range; PE, pulmonary embolism; DVT, deep venous thrombosis; VTE, venous thromboembolism; BMI, body mass index

[a]Extremity DVT includes upper and lower extremity DVTs.

[b]Other VTE were splanchnic vein, inferior vena cava, internal jugular vein, and sinus venous thromboses

[c]Arterial thrombus encompassed ischemic strokes, left ventricular thromboses, left atrial appendage thromboses, ischemic colitis, and Libman-Sacks endocarditis

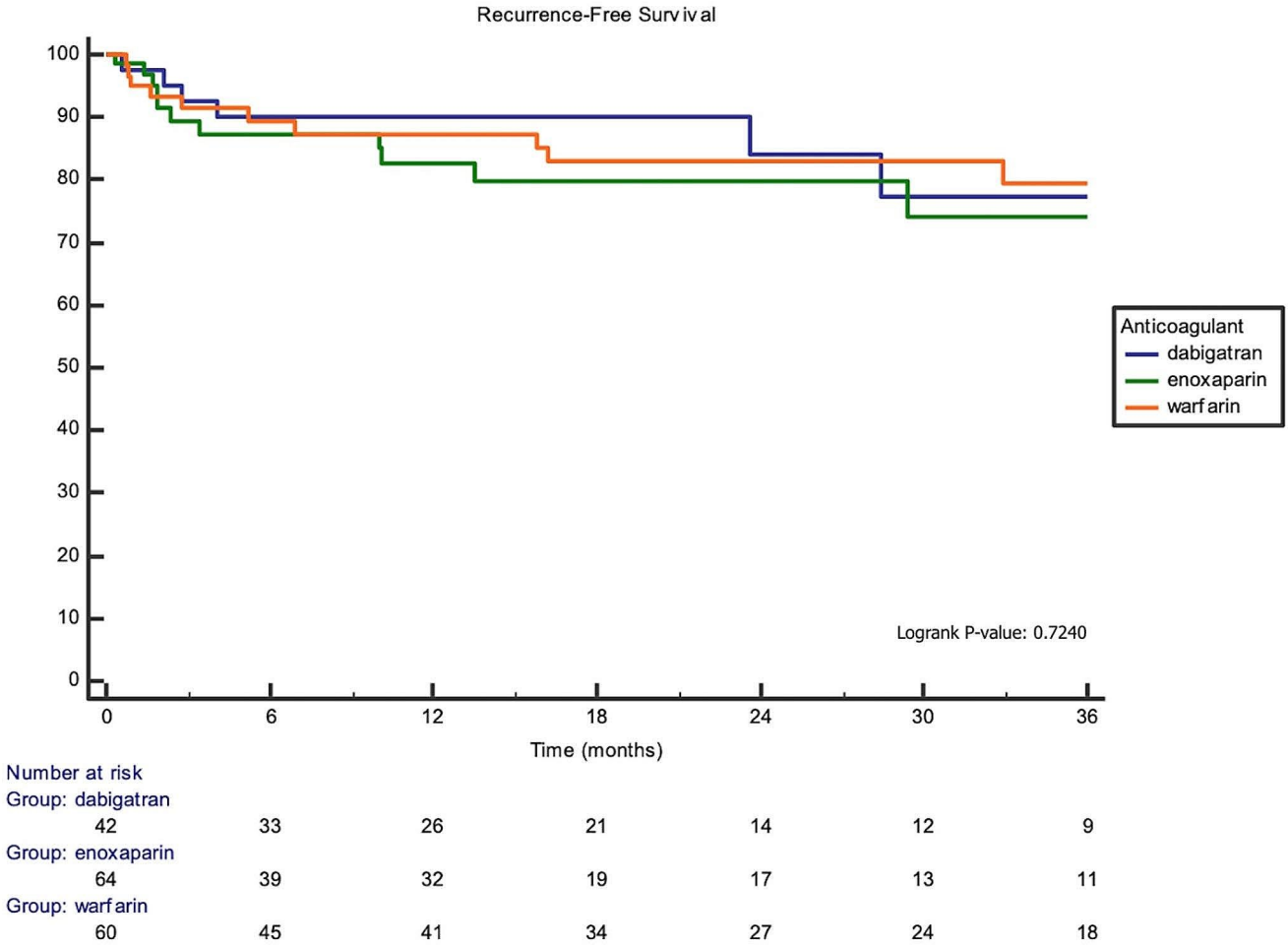

Fig. 1 Kaplan-Meier curve of thrombosis recurrence-free survival after initial thrombosis, compared across second line anticoagulants. There was no statistically significant difference in 2nd recurrent thrombosis-free survival between patients treated with warfarin, dabigatran, or enoxaparin ($p = 0.72$)

recurrent thrombosis-free survival between patients treated with warfarin, dabigatran, or enoxaparin ($p = 0.72$).

In a multivariable Cox model adjusted for both etiology and location of first recurrent thrombosis, dabigatran (HR 0.86, $p = 0.82$) and warfarin (HR 0.90, $p = 0.77$) were not found to be superior or inferior to enoxaparin (Table 2). Additionally, major bleeding occurred in 17 patients (10.2%), and there was no difference in risk of major bleeding events among dabigatran, warfarin or enoxaparin ($p = 0.30$). There was also no significant difference in bleeding events between the malignant and non-malignant groups ($p = 0.24$). Commonly observed reasons for stopping the second line anticoagulant included bleeding episode, 2nd recurrent or persistent unchanged thrombosis, transition to hospice, patient preference (i.e., difficulty with INR checks or subcutaneous administration, insurance coverage), completion of therapy, and procedure event requiring change in therapy.

Discussion

This is the first study to compare outcomes among patients who have recurrent thrombosis while taking a DOAC (apixaban or rivaroxaban) and subsequently switch to a different anticoagulant. Apart from cancer as the etiology of recurrent thrombosis, the three groups (dabigatran, warfarin, enoxaparin) were relatively similar to each other in terms of age, race, DOAC selection, and location of recurrent thrombosis. Among this cohort, there was no difference in thrombosis-free survival or major bleeding among patients subsequently treated with dabigatran, warfarin, or enoxaparin. Thus, any of these anticoagulants are fair options and other factors, such as comorbidities, cost, method of administration, or laboratory monitoring frequency, can be taken into account when selecting a new agent.

Our study demonstrated a 2nd thrombotic recurrence of 16.3% after a change in anticoagulation strategy. This rate is

Table 2 Multivariate analysis by Cox Proportional Hazards Model for etiology of recurrent thrombosis, location of recurrence, and subsequent anticoagulant at recurrence

Variable	HR (95% CI)	*p*-value
Etiology of recurrent thrombosis		
Unprovoked	Reference	0.20
Malignancy	1.99 (0.69 to 5.79)	0.065
Provoked	2.44 (0.95 to 6.28)	
Location of recurrence		
Extremity DVT[a]	Reference	0.16
PE	0.42 (0.12 to 1.41)	0.95
Other VTE	1.10 (0.19 to 5.36)	0.83
Arterial thrombosis	1.15 (0.33 to 3.97)	
Anticoagulation choice at recurrence		
Enoxaparin	Reference	0.82
Warfarin	0.90 (0.36 to 2.25)	0.77
Dabigatran	0.86 (0.30 to 2.45)	

HR, hazard ratio; CI, confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

[a]Extremity DVT includes upper and lower extremity DVTs.

Legend: The results of a Cox proportional hazards model including etiology of recurrent thrombosis, location of recurrent thrombosis, and anticoagulation choice as covariates with respect to risk of second recurrent thrombosis. For each of these covariates option (the most commonly occurring) is used as a reference, to which the other options are compared using hazard ratios (HRs). Notably, none of the covariates were associated with risk of second recurrent thrombosis on this analysis.

higher than the first line failure rates of warfarin, dabigatran, and enoxaparin [11, 12]. This would suggest that patients who fail first line anticoagulation have a higher thrombotic risk, even with a change in therapy, and should be monitored closely for recurrence. Additionally, the major bleeding rate in our study was 10.2%, which is concerning given the patient cohort has a median age of 62. The risks and benefits of anticoagulation should continue to be reassessed in this set of patients.

Past studies have been focused on the safety and efficacy of either switching to enoxaparin after anticoagulation failure or increasing the dose of enoxaparin in patients with malignancy [6, 13, 14]. However, DOACs were not evaluated in these studies given they were done prior to their approval in patients with cancer. The majority of research in this area additionally targets patient with recurrent VTE in the presence of cancer as opposed to all patients who have a recurrent thrombosis, highlighting the novelty of this study. The most similar study to ours focused on patients with DOAC failure who had a brief course of rescue of anticoagulation with enoxaparin before returning to oral anticoagulation, usually another DOAC [9]. This study described the subsequent anticoagulant strategy, however, did not report outcomes such as recurrent thrombosis and bleeding events. There are no prior studies comparing the efficacy of different anticoagulant options used for recurrent thrombosis.

Various guidelines have given clinical expert advice for management in the setting of anticoagulation failure with common options including increasing the dose of anticoagulation, switching anticoagulation or inserting an inferior vena cava filter [15–18]. Of note, they all comment on the lack of evidence in this field and need for further research. We agree with prior expert opinion recommending assessment for factors affecting bioavailability of the DOAC prior to changing to a different anticoagulant, such as adherence, medication interactions and malabsorption [11]. However, in the event that evaluation for etiology of failure is negative, we believe this study provides guidance and reassurance for switching anticoagulation.

Our finding that patients with recurrent thrombosis were significantly more likely to switch to enoxaparin if they had malignancy matched current guidelines and research that supports improved outcomes with enoxaparin and DOACs as opposed to other anticoagulants in the setting of cancer, particularly warfarin [15, 17, 19]. We highlight active malignancy as an example of important patient factors that should continue to be taken into consideration when choosing anticoagulation.

Limitations of our study include its retrospective nature. We looked for documentation and imaging to confirm DOAC adherence, failure and new or worsening thrombosis. Given our strict criteria, we likely did not capture all patients with DOAC failure at our institution. Patients were assumed to be compliant, unless there was a suspicion for nonadherence in the chart, but of course this information may not be true for every patient and reflects reality. Anti-Xa levels are not checked routinely at our institution as the results take several days to report, and thus clinical decisions are made without this data point. Another limitation is the small number of qualifying patients in each arm which was explained by the infrequent occurrence of DOAC failure. Finally, choice of second line anticoagulant was not randomized given the retrospective nature and our data does not capture the nuances in patient care that occur in reality such as patient preference, physician preference, insurance, etc. Other approaches to DOAC failure are not covered by our study due to their infrequent usage at our institution, such as alternative anticoagulants (i.e., fondaparinux, dalteparin, edoxaban) and the addition of ancillary therapies (aspirin, statin, IVC filter).

Our study is the first study to compare anticoagulation options in the setting of DOAC failure. We found that there was no difference in time to recurrent thrombosis or major bleeding among warfarin, enoxaparin, and dabigatran. This topic is even more relevant given the usage of DOAC as the preferred treatment for VTE and the field would benefit from further evaluation to determine the optimal strategies

to reduce risk of recurrent thromboses in this high-risk population through prospective multicenter studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-024-02978-z.

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