Received: 21 February 2024 | Revised: 30 July 2024 | Accepted: 6 August 2024

https://doi.org/10.1016/j.rpth.2024.102546

rpth research & practice in thrombosis & haemostasis

BRIEF REPORT

Dual direct oral anticoagulant therapy in challenging thrombosis: a case series

Nicholas L. J. Chornenki[1] | Heather McPhaden[1] | Erica A. Peterson[1] | Chieh Min Benjamin Lai[1,2] | Agnes Y. Y. Lee[1,2,3]

[1]Division of Hematology, Department of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada

[2]The University of British Columbia Centre for Blood Research, Vancouver, British Columbia, Canada

[3]BC Cancer, Vancouver, British Columbia, Canada

Correspondence
Agnes Y. Y. Lee, Division of Hematology, Department of Medicine, The University of British Columbia, 2775 Laurel Street, 10th Floor, Vancouver, BC V5Z 1M9, Canada.
Email: alee14@bccancer.bc.ca

Handling Editor: Dr Kristen Sanfilippo

Abstract

Background: While anticoagulation therapy is highly effective at treating venous thromboembolism, some patients can develop rapidly progressive thrombosis in multiple organs or sites despite therapeutic anticoagulation. Effective strategies to manage life-threatening thrombosis in these patients are elusive.

Objectives: We describe our experience using dual direct oral anticoagulant (DOAC) therapy with a factor (F)Xa inhibitor (such as rivaroxaban or apixaban) and a FIIa inhibitor (dabigatran) for refractory cases of thrombosis.

Methods: A retrospective chart review of all patients treated with simultaneous dabigatran and an oral FXa inhibitor at our institution was conducted. We included all patients over the age of 18. The study was approved by the University of British Columbia Research Ethics Board (REB number: H23-02575).

Results: Eight patients were included. All patients initiated standard therapeutic anticoagulation upon diagnosis of acute venous thromboembolism with a median of 3 breakthrough thrombotic events prior to dual DOAC use. Five patients had a positive heparin-induced thrombocytopenia screen, but only 2 had heparin-induced thrombocytopenia confirmed on serotonin release assay testing. There were no recurrent deep vein thrombosis, pulmonary embolism, or bleeding events during dual DOAC use. Most patients ultimately transitioned to a single oral FXa inhibitor.

Conclusion: Dual DOAC therapy may be a useful strategy for managing challenging thrombosis cases resistant to conventional anticoagulation. Further research is warranted to validate these findings and explore the broader applicability of dual DOAC therapy in challenging thrombotic scenarios.

Nicholas L. J. Chornenki and Heather McPhaden are cofirst authors.

KEYWORDS
anticoagulation, deep vein thrombosis, direct oral anticoagulant, hypercoagulability, thromboembolism

Essentials

- Effective and safe treatment of refractory venous thromboembolism (VTE) has not been established.
- We treated 8 patients with refractory VTE with a novel combination of 2 blood thinner pills.
- None of the patients had recurrent VTE, bleeding, or death during many months of follow-up.
- Usefulness and safety of this "dual direct oral anticoagulant" strategy for refractory VTE warrants further study.

1 | INTRODUCTION

Venous thromboembolism (VTE) remains a substantial cause of morbidity and mortality despite diagnostic and therapeutic advances over the past decades [1]. While VTE recurrences occurring off anticoagulant therapy are treated with standard anticoagulant regimens, management of refractory VTE events—recurrence while on therapeutic anticoagulation—often involves switching anticoagulants or increasing doses [2]. In some refractory cases, an underlying hypercoagulable state may be identified, such as heparin-induced thrombocytopenia (HIT) that necessitates specific treatment alterations [2,3], but rarely, some patients may follow an extraordinarily accelerated course characterized by progressive thrombosis in multiple organs or sites without a clear etiology. The terms "thrombotic storm," "catastrophic occlusion syndrome," and "devastating noninflammatory vasculopathy" have been used to describe such fulminant cases [4,5]. Small case series suggest these patients tend to be younger, have thrombotic events at unusual sites, and the "storm" is often preceded by a triggering event such as inflammation or infection. Although a variety of interventions have been used, including nonanticoagulant approaches such as plasma exchange and intravenous gamma globulin, effective anticoagulation strategies to manage life-threatening refractory thrombosis remain elusive [6].

Anticoagulation therapy remains the cornerstone for treating acute VTE by inhibiting critical steps in the coagulation cascade [7,8]. Unfractionated and low-molecular-weight heparins (LMWHs) indirectly inhibit multiple coagulation factors by accelerating antithrombin activity, while vitamin K antagonists (VKAs) attenuate the activity of vitamin K–dependent coagulation factors. In contrast, argatroban and dabigatran directly target thrombin, while apixaban, edoxaban, and rivaroxaban block the active site of activated factor (F)Xa [2,8]. Whether multitarget inhibition could be more effective or potent than single-factor specific blockade remains debatable, as randomized trials have demonstrated that a direct oral anticoagulant (DOAC) is effective and comparable with VKAs or LMWH monotherapy for acute VTE treatment [9,10], and yet DOAC is inferior to VKA therapy in mechanical heart valve thrombosis and in antiphospholipid syndrome (APS) [11].

Here, we summarize the experience at our institution with combining 2 DOACs—a direct thrombin inhibitor and a FXa inhibitor—to manage refractory cases of thrombosis that were characterized by treatment failure with 1 or more lines of anticoagulant therapy.

2 | METHODS

A retrospective chart review of patients with refractory thrombosis was conducted at Vancouver General Hospital, Vancouver, Canada, an academic teaching hospital that provides quaternary-level care to residents of British Columbia. We included all patients over the age of 18 who had received dabigatran and an oral FXa inhibitor (apixaban or rivaroxaban) simultaneously following treatment failure with other therapeutic anticoagulant regimens. Data were collected on presenting characteristics, thrombotic history, anticoagulation regimens, and clinical outcomes. This study was approved by the University of British Columbia Research Ethics Board (REB number: H23-02575).

3 | RESULTS AND DISCUSSION

Eight patients (75% male) from 2012 to 2022 with multiple breakthrough thrombotic events despite therapeutic anticoagulation were included. Patients were ages 23 to 69 years (median, 54 years) with a median weight of 99 kg (range, 76-130 kg).

3.1 | Risk factors

At presentation, known thrombotic risk factors included remote history of VTE (2/8), APS (1/8), anabolic steroid use (1/8), homozygous FV Leiden (1/8), oral contraceptive use (1/8), obesity (4/8), and metastatic malignancy (1/8). Two patients with prior VTE were previously stable on long-term therapeutic anticoagulation: one patient was on warfarin for APS and had an International Normalized Ratio of 4.1 prior to the index event, and the other patient was on dabigatran for unprovoked thrombosis. One patient had metastatic lung cancer and was receiving systemic therapy. Two patients presented with the

index VTE after recent exposure to unfractionated heparin; one was exposed in the setting of non-ST elevation myocardial infarction and coronary artery bypass graft, while the other received 6 days of unfractionated heparin thromboprophylaxis during hospitalization. In both cases, HIT was confirmed by serotonin release assay. The remaining patients did not have prior heparin exposure but were tested for HIT when they developed recurrent thrombosis after treatment with unfractionated heparin or LMWH for their index VTE; HIT was excluded by negative HIT enzyme linked immunosorbent assay or serotonin release assay results. During their course, none of the cohorts were diagnosed with APS (although lupus anticoagulant could not be measured because all patients were on high doses of anticoagulants), and none were identified with occult malignancy.

3.2 | Refractory thrombotic events and management

Index thrombotic events comprised deep vein thrombosis (DVT; 8/8), pulmonary embolism (PE; 7/8), bilateral lower limb arterial ischemia with aortic thrombus (1/8), and cerebral venous thrombosis (1/8). For the index event, patients were started on therapeutic anticoagulation with LMWH (4/8), unfractionated heparin (2/8), apixaban (1/8), or fondaparinux (1/8). Upon diagnosis of a new site of VTE or extension of existing thrombus, therapy was modified by either dose escalation of the same anticoagulant or changing to an alternate anticoagulant. The median time from index event to first recurrence was 19 days (range, 3-49 days). There were a median of 3 (range, 1-5) subsequent lines of therapy prior to dual DOAC therapy initiation. Four patients who were receiving argatroban were first placed on an oral FXa inhibitor concomitantly and then were switched from argatroban to dabigatran while continuing the oral FXa inhibitor. Individual patient treatment trajectories for the 8 patients are depicted in Figure 1, and the maximal doses and duration of parenteral anticoagulation used are provided in Table 1. The patient with arterial thrombosis also remained on acetylsalicylic acid 81 mg daily. In addition, invasive procedures were attempted, including catheter-directed thrombolysis (2/8), mechanical thrombectomy (1/8), and inferior vena cava filter insertion (1/8). The maximal D-dimer at the time of recurrent events ranged from 4000 to 34,191 μg/L fibrinogen equivalent unit (median, 10,296 μg/L fibrinogen equivalent unit), excluding values drawn after thrombolysis. Upon initiation of dual DOAC therapy, D-dimer decreased by a median of 34% within 5 days (range, 25%-50%).

3.3 | Follow-up courses

After dual DOAC therapy was initiated, there were no further breakthrough venous thrombotic events, and all patients were discharged from hospital on dual DOAC therapy with dabigatran and either apixaban (2/8) or rivaroxaban (6/8) as the second DOAC. Table 2 outlines the initial and longer-term anticoagulation regimens of the 8 patients.

Dual DOAC treatment was continued for a minimum of 1 month (range, 1-103 months), except for 1 patient who discontinued dabigatran after 1 day due to dyspepsia and continued on rivaroxaban therapy alone. Of the remaining 7 patients, 5 patients later transitioned to a single oral FXa inhibitor, while 1 continued dabigatran alone. One

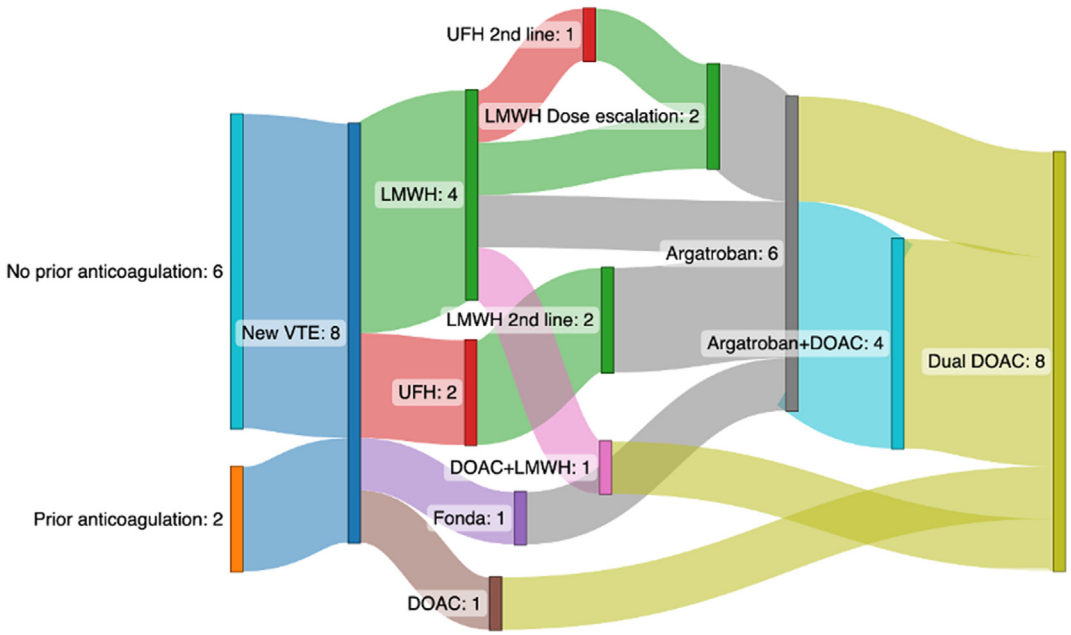

FIGURE 1 Anticoagulation treatment trajectories for individual patients. Note: numbers represent the number of patients on each specific therapy. Each section indicates a specific anticoagulation regimen, and paths are not to a time scale. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

TABLE 1 Parenteral anticoagulation prior to dual direct oral anticoagulant use.

Patient	Anticoagulant (maximum dose given)	Duration (d)[a]	aPTT range while on UFH Peak anti-Xa at 4 h after LMWH
1	Dalteparin (310 U/kg/d)	23	Anti-Xa: 0.55 U/mL
	UFH (18 U/kg/h)	<1	aPTT 66 s
	Argatroban (4 μg/kg/min)	12	aPTT 51-82 s
2	Fondaparinux 10 mg/d	1	NA
	Argatroban (6 μg/kg/min)	31	aPTT 59-90 s
3	Dalteparin (220 U/kg/d)	13	NA
	Fondaparinux 7.5 mg/d	18	NA
	Argatroban (13.4 μg/kg/min)	32	aPTT 66-91 s
4	No parenteral anticoagulation		NA
5	Nadroparin (250 U/kg/d)	20	NA
	UFH (28 U/kg/h)	7	aPTT 45-119 s
	Dalteparin (384 U/kg/d)	4	Anti-Xa: 0.53 U/mL
	Argatroban (11.2 μg/kg/min)	44	aPTT 80-100 s
6	Dalteparin (192 U/kg/d)	58	Anti-Xa: 0.70 U/mL
	UFH (19 U/kg/h)	1	aPTT 117-140 s
7	UFH (18 U/kg/h)	5	aPTT 62-88 s
	Enoxaparin (2.6 mg/kg/d)	5	NA
	Argatroban (6.5 μg/kg/min)	12	aPTT 67-105 s
8	Dalteparin (200 U/kg/d)	1	NA
	UFH (dose unavailable)	6	aPTT > 140 s
	Argatroban (11 μg/kg/min)	51	aPTT 69-130 s

PTT, as a range while on therapy, is reported in seconds. Anti-Xa are peak levels drawn 4 hours after administration and are reported in units per milliliter. PTT or anti-Xa levels were sometimes NA in some cases where the patient was transferred from another institution.

LMWH, low-molecular-weight heparin; NA, not available; PTT, partial thromboplastin time; UFH, unfractionated heparin.

[a]Duration corresponds to the total duration of exposure to an anticoagulant, not necessarily the duration at the maximal dose.

patient was on dual DOAC therapy for up to 100 months at the last follow-up. During dual DOAC therapy, 1 patient had superficial thrombophlebitis at 54 months and 1 patient had an arterial thrombotic event at 3 months. Another 2 patients experienced subsequent thrombotic events at 1 month and 71 months after dual DOAC cessation; both had arterial events (stroke and ischemic limb) while on a single anticoagulant. The median follow-up time was 32 months (range, 6-103 months). None of the patients died during follow-up.

The course of the first patient who received dual DOAC treatment is illustrated in Figure 2. This previously healthy patient presented with left leg DVT following a minor leg injury. While on dabigatran, he developed symptomatic cerebral venous thrombosis. He was admitted and placed on heparin infusion followed by LMWH nadroparin. He then experienced bilateral PE and right leg DVT. Despite a 20% increase in his LMWH dose, he had a progression of PE and was switched back to heparin infusion. While maintaining therapeutic activated partial thromboplastin time (aPTT) values, he had 2 episodes of near cardiac arrest due to right atrial thrombus and progressive PE. HIT was excluded by enzyme linked immunosorbent assay. Catheter-directed thrombolysis was performed on both occasions, and an inferior vena cava filter was inserted. He was then switched to argatroban but developed a right arm DVT and bilateral renal infarcts days later. Acetylsalicylic acid 81 mg was added. Between days 60 and 80, he required increasingly higher and higher doses of argatroban to maintain therapeutic aPTT values. When he reached an argatroban dose of 11.3 μg/kg/min, rivaroxaban 15 mg twice daily was added on day 85 with the aim to reduce thrombin generation and reduce argatroban requirement. As illustrated, thrombin-antithrombin levels sharply dropped with the addition of rivaroxaban and argatroban dose was successfully tapered. D-dimer also continued to trend downward. On day 106, argatroban infusion was turned off and dabigatran 150 mg twice daily was started. The patient remained on dabigatran and rivaroxaban for the next 1.5 months and eventually continued rivaroxaban 20 mg once daily indefinitely. At 7 months after initial presentation, he was asymptomatic and serial imaging studies showed near-complete thrombus

TABLE 2 Anticoagulation regimens of 8 patients receiving dual direct oral anticoagulant therapy.

Thrombin inhibitor	Factor Xa inhibitor	Dual DOAC duration	Subsequent treatment
Dabigatran 150 mg twice a day	Rivaroxaban 20 mg once daily	1 mo	Rivaroxaban 20 mg once daily
Dabigatran 150 mg twice a day	Apixaban 10 mg twice a day	4 mo	Apixaban 5 mg twice a day
Dabigatran 110 mg twice a day	Rivaroxaban 20 mg once daily	1 d	Rivaroxaban 20 mg once daily
Dabigatran 150 mg twice a day	Apixaban 10 mg twice a day	3 mo	Apixaban 5 mg twice a day
Dabigatran 150 mg twice a day	Rivaroxaban 15 mg twice a day	1.5 mo	Rivaroxaban 20 mg once daily
Dabigatran 220 mg twice a day	Rivaroxaban 15 mg twice a day	103 mo	Dabigatran 150 mg twice a day and rivaroxaban 20 mg once daily
Dabigatran 150 mg twice a day	Rivaroxaban 15 mg twice a day	1 mo	Rivaroxaban 20 mg once daily
Dabigatran 150 mg twice a day	Rivaroxaban 20 mg twice a day	3 mo	Dabigatran 150 mg twice a day

DOAC, direct oral anticoagulant.

resolution. Testing for heritable thrombophilia, FVIII level, antiphospholipid antibodies, malignancy, *JAK2* V617F mutation, and paroxysmal nocturnal hemoglobinuria were negative. The only potential thrombotic risk factor was the excessive use of anabolic steroids within 3 months prior to initial presentation.

3.4 | Comments

The above cases provide anecdotal evidence that the use of dual DOAC anticoagulation in the acute setting is a potentially safe and effective strategy in patients with refractory thromboses. By inhibiting both FXa and thrombin, dual DOAC therapy "mimics" the mechanism of LMWH, but it does not rely on endogenous antithrombin, which might be substantially reduced in fulminant cases of thrombosis through consumption [12]. Biochemically, combining FXa and thrombin inhibition likely enhances the anticoagulant effect by reducing thrombin generation as well as suppressing any positive cascade feedback from thrombin that is already generated [13]. Furthermore, dabigatran is more effective in inhibiting clot-bound thrombin than heparin or LMWH [14]. The marked reduction in D-dimer observed in our cases when dual DOAC was initiated provides indirect evidence that clot formation was effectively attenuated.

An advantage of our newly described therapeutic regimen compared with parenteral anticoagulation is that DOACs have predictable pharmacokinetics and do not require aPTT-based or weight-adjusted dosing [8]. Additionally, these oral agents have approved reversal agents, which may further enhance their safety and utility

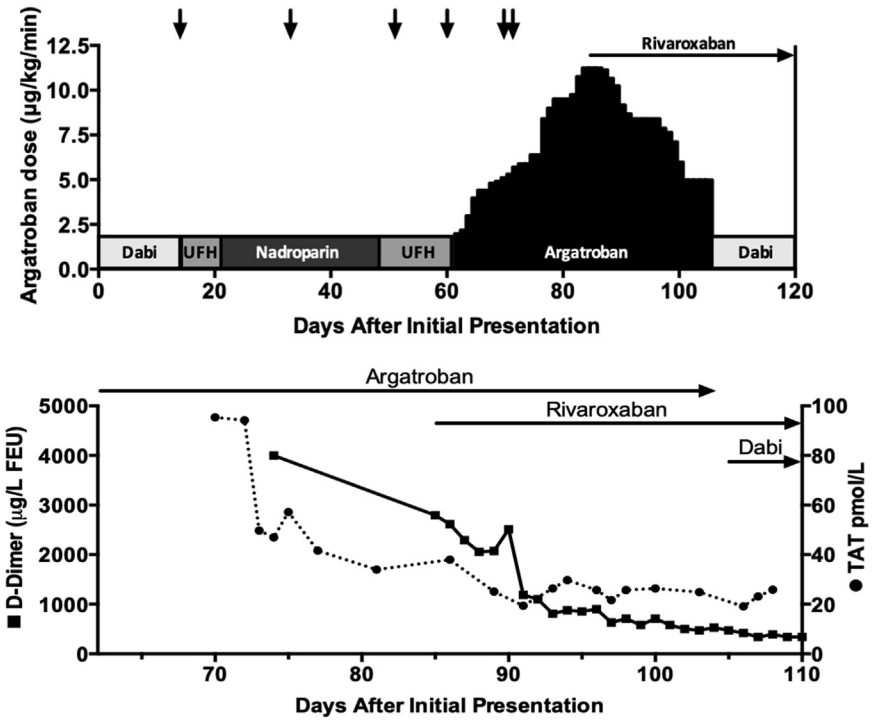

FIGURE 2 Example of patient treatment course recording argatroban dose, D-dimer, and thrombin-antithrombin (TAT) complex responses to dual direct oral anticoagulant. Short vertical arrows in top graph represent breakthrough thrombotic events. Dabi, dabigatran; FEU, fibrinogen equivalent unit; UFH, unfractionated heparin.

[15]. It is worth noting that in half of our cases, high argatroban doses were needed to achieve therapeutic aPTT values prior to dual DOAC use. In addition to being ineffective, the high doses of argatroban represented a substantial bleeding risk to the patients. The addition of an oral FXa inhibitor allowed lowering of argatroban doses and then later substitution of argatroban with dabigatran. Based on our experience, it might be reasonable to introduce dual DOAC therapy without using parenteral anticoagulation initially to manage cases of fulminant, refractory thrombosis. Interestingly, the recurrent thrombotic events during follow-up were mainly arterial, but the numbers are too small to draw any conclusions.

While common causes of hypercoagulability such as HIT, cancer, and APS were present in some of our patients, we cannot exclude the possibility of more recently identified prothrombotic conditions, such as other PF-4–mediated thrombotic disorders [16]. Our cases occurred in the pre–COVID-19 era, and we did not routinely test for *JAK2* mutation or have lupus anticoagulant results to exclude APS. Another limitation of this study is that drug levels for LMWH and DOACs were not available at the time of recurrent events, largely because the timing of when recurrences were diagnosed usually did not correspond to when peak or trough levels could be drawn and interpreted. Our center also did not measure DOAC levels during most of the study period. Where available, aPTT measurements and anti-Xa levels are reported in Table 1.

To our knowledge, this is the first report of a strategy using an oral direct thrombin inhibitor and an oral FXa inhibitor simultaneously to target separate activated coagulation factors for treatment of refractory thrombosis. While our cohort shows that dual DOAC therapy was well tolerated, our experience is based on a small observational series of 8 patients. We encourage further research to strengthen these findings and explore the broader applicability of dual DOAC therapy in challenging thrombotic scenarios.

FUNDING

The authors received no funding for this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, acquisition, analysis, and interpretation of data and critically revised the manuscript for important intellectual content. N.L.J.C. and H.M. wrote the first draft of the manuscript. N.L.J.C. and E.A.P. developed the figures. All authors gave final approval of the submitted manuscript.

RELATIONSHIP DISCLOSURE

N.L.J.C., H.M., and E.A.P. have nothing to declare. C.M.B.L. receives partial salary support from the Sheldon Naiman and Linda Vickars Endowment Fund. A.Y.Y.L. has received honoraria for consultancy from Bayer, Bristol-Myers Squibb, LEO Pharma, Janssen, and Pfizer.

ORCID

Agnes Y. Y. Lee https://orcid.org/0000-0003-1915-6681

X

Nicholas L.J. Chornenki @NicholasJC95

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