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ORIGINAL ARTICLE

Delayed anticoagulation in venous thromboembolism: Reasons and associated outcomes

Nichole E. Brunton DO[1] | Waldemar E. Wysokinski MD, PhD[2] | David O. Hodge MS[3] | Danielle T. Vlazny PA-C MS[2] | Damon E. Houghton MD, MS[2] | Ana I. Casanegra MD, MS[2]

[1]Department of Internal Medicine, Danbury Hospital, Danbury, CT, USA

[2]Department of Cardiovascular Medicine Division of Vascular Medicine, Gonda Vascular Center, Mayo Clinic, Rochester, MN, USA

[3]Department of Health Sciences Research, Mayo Clinic, Jacksonville, FL, USA

Correspondence
Ana I. Casanegra, Gonda Vascular Center, Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street, Rochester, MN 55905, USA.
Email: casanegra.ana@mayo.edu

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Abstract

Objective: We assessed the number of cases with delayed anticoagulation initiation, explored the reasons for the delay, and its impact on outcome in patients with acute venous thromboembolism (VTE) treated in an organized setting of treatment initiation and continuous, prospective follow-up.

Methods: Patients with anticoagulation initiation delay >24 hours were identified within the cohort of patients with acute VTE enrolled in the Mayo Clinic Venous Thromboembolism Registry between 2013 and 2020. The reasons for treatment delay were explored by reviewing the electronic database. VTE recurrence, all-cause mortality, major bleeding, and clinically relevant nonmajor bleeding (CRNMB) were compared to those with no anticoagulation delay.

Results: Of 2378 patients with acute VTE, 100 (4.2%) experienced an anticoagulation delay. We identified seven reasons for treatment delays: deferring anticoagulation initiation to specialists (n = 38), thrombocytopenia (n = 10), planned or recent procedure (n = 16), active or recent bleeding (n = 12), missed diagnosis (n = 7), logistics (n = 6), and patient decision (n = 4). In seven cases, no reason was identified. We identified modifiable reasons for anticoagulation delay in 55%. At 90-day follow-up, patients with anticoagulation delay had a higher rate of mortality and major bleeding. VTE recurrence and CRNMB were not statistically different compared to those without anticoagulation delay. After adjustment for age, weight, and cancer, hazard ratios (HRs) for VTE recurrence and major bleeding remained elevated but not to a statistically significant level.

Conclusion: In the setting of a highly organized system of anticoagulation initiation, the incidence of treatment delay is low. Yet most delays could be avoided. A low number of cases provide insufficient power to evaluate the clinical consequences of anticoagulation initiation delay; however, elevated HR for VTE recurrence and major bleeding suggest association and need for further investigation.

KEYWORDS
anticoagulant, neoplasm, recurrence, registry, time to treatment, venous thromboembolism

Essentials

- Blood clots are treated promptly with anticoagulation; we investigated reasons for care delay.
- The study was completed at the Mayo Clinic Thrombophilia Clinic in Rochester, Minnesota.
- We found eight causes for care delay; the most common was referral to a specialist.
- Care delays should be avoided; future studies to evaluate outcomes related to delays are needed.

1 | INTRODUCTION

Venous thromboembolism (VTE) impacts approximately 75 to 296 cases per 100 000 people annually worldwide.[1-3] It is established that early identification and prompt initiation of anticoagulation therapy is critical for the prevention of clot propagation and reduction in mortality.[1,2,4,5] Current guidelines recommend immediate initiation of anticoagulation therapy not only for confirmed cases but also highly suspected cases of VTE when the potential complication risk from bleeding is considered acceptable. Clinicians and patients face numerous challenges regarding anticoagulation initiation following VTE diagnosis such as bleeding risk, out-of-pocket cost of anticoagulation, availability of reversal agents, the prospect of compliance, underlying comorbidities, and duration of therapy.[1,6,7] In addition, different clinical presentations such distal (calf) deep vein thrombosis (DVT), subsegmental pulmonary emboli (PE), and VTE of atypical location create another level of complexity in clinical decision making.[8–11]

While the importance of promptly starting anticoagulation is well known, less is known on current practices of anticoagulation initiation, causes of anticoagulation delay, and predictors of anticoagulation deferral or abstention. Anticoagulation delays may occur due to the complicated nature of treating VTE events, coexisting conditions, or different clinical presentations. The first aim of this study was to identify cases with delayed time to treatment with anticoagulation and characterize the reasons for the delay. A second aim was to determine if delayed initiation of anticoagulation therapy was associated with adverse clinical outcomes.

2 | METHODS

Consecutive patients requiring anticoagulation for VTE events were enrolled prospectively into the Mayo Clinic Venous Thromboembolism Registry (ClinicalTrials.gov: NCT03504007) from March 1, 2013, to March 31, 2020. The Thrombophilia Clinic at the Gonda Vascular Center in Rochester, Minnesota, provided a systematic method for the management of patients with VTE, with the goal of expedited access for appropriate and timely management of patients with VTE.[11] Participants included in the VTE Registry initiated anticoagulation therapy within 14 days of diagnosis of VTE; those not initiating therapy or with profoundly delayed initiation (>14 days) were excluded. Patients arrived through different pathways, including direct same-day referral from radiology after finding an acute VTE and referral from providers after initial treatment, from both the outpatient and inpatient setting. All patients included were evaluated at the Thrombophilia Clinic within 14 days of the initial VTE diagnosis. Thrombophilia clinic providers and patients decided on the most appropriate anticoagulant agent for initial or subsequent treatment using a shared decision-making tool that includes a patient-specific analysis of comorbidities, personal preferences, and medication cost. The clinic could administer a single dose of low-molecular-weight heparin (LMWH) if needed until the patient obtained the anticoagulant prescription. An on-site pharmacy was available for ease of obtaining the prescribed medications. We included all first VTE events (DVT of the upper and lower extremities, PE and VTE in atypical locations). The only exclusion criteria were the presence of an isolated calf DVT, as anticoagulation is not mandatory. Patients who did not sign an authorization for research were not included in this analysis. The study was approved by the Mayo Clinic Institutional Review Board.

2.1 | Outcome measures and study definitions

For the primary aim of the study, determining causes for delay in time to treatment with anticoagulation therapy in acute thrombotic events, we defined anticoagulation delay as the time to treatment with anticoagulation beyond 24 hours after the initial diagnosis of VTE. Initiation of therapy included treatment with anticoagulation including intravenous heparin infusion, LMWHs, direct oral anticoagulants, or warfarin with LWMH or heparin bridge. The time of diagnosis was considered the time of the first positive imaging study confirming the VTE event, with the expected initiation of anticoagulation within 24 hours. Anticoagulation therapy initiation was defined as the time difference between the initial radiographic study confirming VTE and the date/time of prescription or administration of anticoagulant medication. Patients receiving their first administration of anticoagulation (confirmed by documentation in the medication administration record and prescription history) >24 hours after the radiographic study were considered as having

delayed initiation of therapy. All patients with treatment delay underwent a thorough chart review to determine the etiology of the delay. As the chart reviews for delayed cases were completed, similar events were grouped into categories including repetitive themes for analysis.

The secondary aim of the study was to investigate primary safety and efficacy outcomes at 90 days in the patients experiencing an anticoagulation delay in comparison to those with no anticoagulation delay. Adverse outcomes reported include major bleeding events, clinically relevant nonmajor bleeding (CRNMB) events, recurrent VTE, and all-cause mortality. In accordance with the ISTH, major bleeding was defined as an overt bleed with concurrent hemoglobin decrease of ≥2 g/dL or requiring transfusions of ≥2 units of packed red blood cells, bleeding in critical areas (intraocular, intraspinal, intracranial, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome) or fatal bleed.[12,13] CRNMB events were defined as a bleeding event not meeting criteria for major bleed but prompting temporary cessation in therapy or an unscheduled interaction with medical personnel. Recurrent VTE was defined as any VTE involving a new segment as previously described.[8] All events were adjudicated by review of the medical record by three thrombosis specialists (physician or physician assistant), using previously defined study criteria.[12,13] Discrepancies between reviewers were solved by a secondary review of the medical record and a face-to-face discussion between the adjudicators until reaching a consensus. Adjudication was blinded to the timing of initiation of anticoagulation.

Atypical location of thrombus was defined as any thrombus not involving the extremities or pulmonary vasculature (defined as cerebral sinus vein thrombosis or splanchnic, gonadal, or renal vein thrombosis). PE was classified as incidental (if the test was done for a different indication than suspected PE or symptoms suggestive of PE) or symptomatic if they were done for suspected PE, to rule out a PE or if the patient presented clinical signs or symptoms suggestive of PE at the time of diagnosis.

2.2 | Surveillance, follow-up, and data collection

After the initial evaluation, patients were scheduled for a 90-day follow-up appointment at the same thrombophilia clinic. During the scheduled follow-up appointment, patients were assessed in person for complications. If a face-to-face encounter was not feasible, then a follow-up questionnaire was used by scripted telephone encounter or mailed through the postal service. In-person or non–face-to-face follow-ups were performed at 6 months and 1 year as part of the registry.

The medical records of patients with suspected delayed onset of anticoagulation were reviewed by two of the authors (AIC and NEB), which corroborated the anticoagulation starting time and the reasons for the delay. The reasons for the delay were grouped by themes after the abstraction of data was completed. As the registry was curated before this study, including data on clinical outcomes, chart reviewer bias for anticoagulation delay was minimized. The authors (AIC and NEB) were also blinded to patient outcomes during chart review for anticoagulation initiation time and reasons for delay.

2.3 | Statistical analysis

Baseline data were reported as a percentage of the total or as a median and interquartile ranges. Each of the baseline continuous variables in Table 1 were tested for normality using the Kolmogorov-Smirnov test and were determined to have some evidence that they were nonnormal. The no-anticoagulation-delay and anticoagulation-delay groups were tested for statistically significant differences using the Wilcoxon rank-sum test or Pearson chi-squared test, if categorical. Logistic regression models were used to evaluate the 90-day outcomes while adjusting for age, weight, and presence of cancer in the comparison of no-anticoagulation-delay and anticoagulation-delay groups. Follow-up outcomes were estimated using the Kaplan-Meier method. Summaries of these outcomes were also provided using the person-years approach. The Fine and Gray method was used to evaluate the outcomes using death as a competing risk for the event of interest. Comparisons of mortality between groups were completed using the log-rank test. Of note, only 6.7% of patients enrolled prospectively were lost to in-person follow-up and therefore excluded from the final analysis. In subjects ultimately included (n = 2378), <1% were missing demographic data in all categories. The analysis was completed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

During the study period, 2378 patients were enrolled and followed prospectively. One hundred seventy-eight patients did not sign the authorization for research and were excluded from the analysis. Among enrolled patients, 100 (4.2%) experienced a documented anticoagulation delay. Compared with the prompt-anticoagulation group, there were no significant differences in age, sex, renal function, or platelet count (Table 1). Patients in the anticoagulation-delay group did have a higher incidence of active neoplasms compared to the prompt-anticoagulation group patients (difference, 16.9%; 95% confidence interval [CI], −23.7 to 10.2), but fewer patients with malignancy in the delayed-anticoagulation group were actively receiving chemotherapy. The malignancy types were not different between the two groups (Table 1).

The initial choice of anticoagulation medication differed between the two groups of the study. The anticoagulation-delay group was found to use apixaban more commonly as the first choice of treatment (32.0%) in comparison to 15.4% in the prompt-anticoagulation group. Meanwhile, the prompt-anticoagulation group used heparin

more frequently (24.5%) when compared to the anticoagulation-delay group (10.0%). Usage of LMWH was similar between the two groups (46.7% vs 46.0%).

The anticoagulation-delay group experienced a significantly higher rate of provoked VTE events compared to the prompt-anticoagulation group (93% vs 79.8%, 95% CI of the difference, 16.9, 9.5), mainly because of the higher prevalence of malignancy in the first group (Table 1). Recent surgery, confinement, trauma, thrombophilia, and hormone therapy were evenly distributed between the two groups (Table 1).

Patients with anticoagulation delay had a higher incidence of VTE of atypical location compared to the prompt-anticoagulation-initiation group (46% vs 17%, 95% CI, 22-36). Patients from the anticoagulation-delay group were more likely to have incidental PE when compared with the prompt-anticoagulation group (Table 1).

3.2 | Distribution and causes of delayed time to treatment

Seven key reasons for anticoagulation delay were identified as repetitive themes and grouped as follows: (i) *referral for expertise*, when the decision to start anticoagulation or not was deferred to an expert in thrombosis; (ii) *thrombocytopenia*, when the treating physician documented low platelets as the reason for not initiating anticoagulation; (iii) *active or recent bleeding*, when anticoagulation was not initiated due to ongoing bleeding or recently resolved bleeding with high risk of recurrence; (iv) *recent or planned surgery/procedure*, when the delay was due to an upcoming surgery or procedure in the following days or a surgery in the previous day that would require hemostasis; (v) *missed diagnosis*, when the results of the imaging study were not reviewed or not acted upon within the 24-hour frame; (vi) *logistics*, when, despite having a

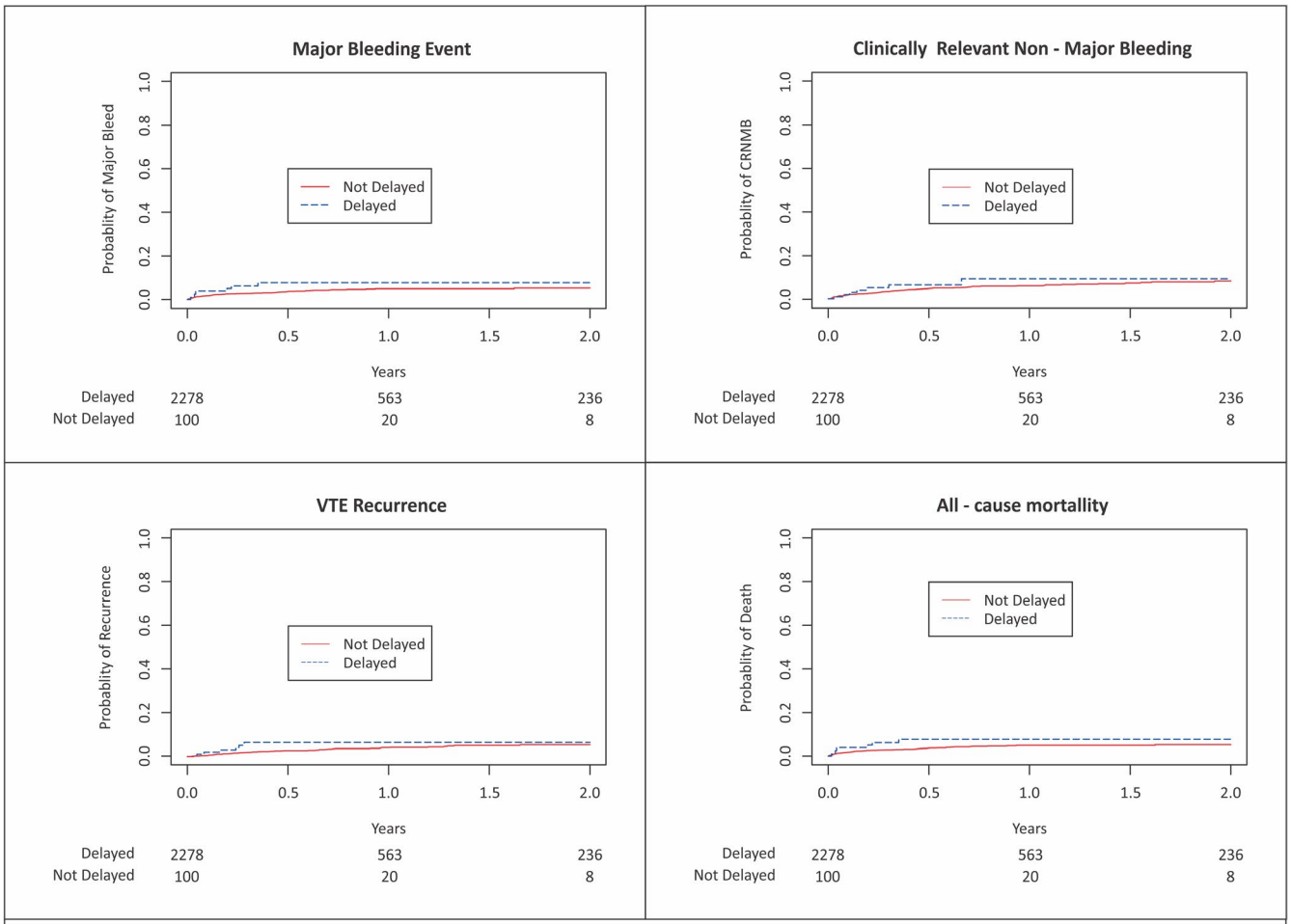

FIGURE 1 Kaplan-Meier curves for associated outcomes in patients with delayed onset of anticoagulation versus those with prompt initiation of anticoagulation

provider prescribing the anticoagulant and a patient willing to take it, the anticoagulation did not happen until after 24 hours; and (vii) *patient choice*, when there was documentation that the patient declined starting anticoagulation.

The most common reason for the anticoagulation delay was to defer the decision to a provider with expertise in thrombosis, occurring in 38 cases. Subsequent common causes included recent or planned surgery or procedure (n = 16), active or recent bleeding (n = 12), and thrombocytopenia (n = 10). Less common causes included missed diagnosis (n = 7), logistics (*n* = 6), and patient choice (n = 4). After review, 55% of cases were considered modifiable causes due to delay for referral, missed diagnosis, logistics, and initial patient decision. In seven cases, we could not identify a documented rationale for delay in anticoagulation therapy.

3.3 | Clinical outcomes

At 90 days, there was higher all-cause mortality (10% vs 5%; HR, 2.11; 95% CI, 1.07-4.16) and major bleeding (6% vs 2.7%; HR, 2.28; 95% CI, 1.00-5.41) in the anticoagulation-delay group compared with the patients with prompt anticoagulation initiation. VTE recurrence and CRNMB events occurred similarly between the anticoagulation-delay and prompt-anticoagulation groups (Figure 1).

When we compared events per 100 patient-years (Table 2), the major bleeding rate was 11.3 versus 4.7 per 100 patient-years for the anticoagulation-delay group and those with prompt anticoagulation, respectively (HR, 2.2; 95% CI, 1.07-4.54). VTE recurrence and CRNMB events were not different when reported per 100 patient-years and after accounting for competing risks. After adjustment for age, weight, and malignancy, differences between the two groups were not statistically significant for the outcomes of recurrence, major bleeding event, or CRNMB. It should be noted, however, that HRs remained elevated for both major bleeding and VTE recurrence after adjustment.

Mortality was higher in the anticoagulation-delay group (57.6 vs 31.3 per 100 patient-years; HR, 1.94; 95% CI, 1.42-2.64). This was true even after adjustment for age, weight, and presence of cancer.

4 | DISCUSSION

In our organized system of prompt patient referral, therapy initiation, and controlled follow-up, the incidence of anticoagulation initiation delay by more than 24 hours is small (4.2%), yet more than half of the time, therapy delays could be potentially prevented. Given the need for prompt anticoagulation to improve clinical outcomes, it is important to minimize delays when possible.[2,4,9,14]

To our knowledge, this is the first study examining the causes of true anticoagulation delay. Current studies focus on the noninitiation of anticoagulation therapy. These include reports based in Denmark, Canada, and the United States, and have a larger reported incidence of 24% to 40%.[15–17] While this may help to understand noninitiation of therapy for VTE and identifying patients at risk, it fails to examine the reasons for withholding anticoagulation or delays in initiation of anticoagulation.[16–18]

The most frequent reason for the delay was deferring initiation of anticoagulation until obtaining expert advice for in-person expert consultation (n = 38). These delays occurred in the absence of high bleeding risk and were surprising given 24/7 accessibility of an on-call vascular physician, and availability of same-day appointments.

Two main subgroups of patients appeared to comprise the delay for specialist referral category: those with VTE of atypical location and those with underlying malignancy. Twenty of 38 of the patients (52%) with anticoagulation delay for specialist referral were diagnosed with VTE of atypical location, underscoring the uncertainty in general practitioners or other subspecialties regarding optimal treatment. This is highlighted by conflicting societal guidelines.[19,20] Due to a paucity of current knowledge for the treatment of VTE of atypical location, it is not surprising that they result in a delay for specialist referral. Additionally, delay for specialist referral occurred frequently with patients with underlying malignancy. This population carries a higher risk of bleeding due to tumor-associated bleeding or side effects from chemotherapy agents, such as thrombocytopenia.[21,22] Patients with malignancy have increased rates of VTE of atypical location[23] and incidental PE, which may contribute to increased requests for expert assistance due to the lack of evidence-based guidelines. It is expected that decision making would be complex in this population.

Other modifiable reasons include logistics, patient decision, and missed diagnosis. In the instance of logistics (n = 6), events included transition between medical institutions and delays in obtaining records, delays on education for self-injection, and scheduling errors. Missed diagnosis occurred due to delays in reviewing the imaging report or physician error in interpretation of radiographic studies (n = 7). A thorough evaluation of these event types as reportable incidents should be considered to determine root cause analysis with a plan to address them on a system level to prevent similar future events.

The patient decision, even though uncommon (4% of the delayed anticoagulation), occurred secondary to financial barriers or personal concerns. All patients included eventually started anticoagulation, suggesting they needed more time to process the information or that the patient-centric, shared decision-making tool used in the clinic aided in their choice. Improvements in patient education, pharmacy support, and social work assistance could help minimize these instances. Since our registry included only patients starting anticoagulation within 14 days of diagnosis, it is unclear how many patients ultimately refused anticoagulation.

Meanwhile, a significant portion of the study population was unable to initiate timely therapy due to non-modifiable causes. Importantly, 38% of the study population was unable to initiate therapy due to active bleeding or a perceived increase in bleeding risk. This includes patients with thrombocytopenia (n = 10), active/recent bleed (n = 12), or periprocedural status (n = 16). Perioperative/periprocedural status encompassed patients in the immediate postoperative peiod deemed unsuitable for anticoagulation due to inadequate hemostasis or patients with planned surgical interventions

TABLE 1 Comparison of demographic characteristics of patients with delays in anticoagulation therapy >24 hours from diagnosis versus those with no delays

Variable	Delay n = 100	No delay n = 2278	Difference (95% CI)
Age, y, median (IQR)	64 (56-71)	63 (53-71)	−1 (−3 to 1)
Female sex, n (%)	45 (45.0)	994 (43.6)	1.4 (−5.7 to 8.4)
Weight, kg, median (IQR)	80.0 (68.5-96.0)	87.3 (72.8-102.0)	7.3 (2.6 to 12.0)
Time to anticoagulation initiation, d, median (IQR)	4 (2-7)	0 (0-0)	
VTE location, n (%)			
DVT and PE	54 (54.0)	1891 (83.0)	29 (22 to 36)
Splanchnic	25 (25.0)	137 (6.0)	−19 (−25 to −13)
Portal	21 (21.0)	97 (4.3)	−17 (−22 to −11)
Splenic	4 (4.0)	20 (0.8)	−3.2 (−5.9 to −0.4)
Gonadal	8 (8.0)	37 (1.6)	−6.4 (−10.2 to −2.6)
Cerebral venous	10 (10.0)	58 (2.5)	−7.5 (−11.7 to −3.3)
Provoked, n (%)	93 (93.0)	1816 (79.8)	−13.2 (−16.9 to −9.5)
Recent surgery	14 (14.0)	391 (17.2)	3.2 (−1.8 to 8.1)
Malignancy	65 (65.0)	1095 (48.1)	−16.9 (−23.7 to −10.2)
Confinement	6 (6.0)	318 (14.0)	8.0 (4.5 to 11.4)
Thrombophilia	2 (2.0)	45 (2.0)	0 (−2.0 to 2.0)
Trauma	5 (5.0)	106 (4.7)	−0.3 (−3.4 to 2.7)
Hormone therapy/pregnancy	3 (3.0)	88 (3.9)	0.9 (−1.6 to 3.3)
Baseline characteristics			
Incidental PE, n (%)[a]	26 (72.2)	466 (38.6)	−33.6 (−40.0 to −27.2)
Receiving chemotherapy, n (%)[b]	34 (54.0)	689 (64.0)	10.1 (3 to 17.1)
Previous history of VTE, n (%)	22 (23.4)	472 (21.9)	−1.5 (−7.5, 4.5)
Platelet count, median (IQR)	222 (166-289.5)	223 (168-290)	1 (−29 to 41)
Platelets <50 × 10^9/L, n (%)	9 (9)	23 (1)	
Platelets 50-75 × 10^9/L, n (%)	3 (3)	36 (1.6)	
Platelets 75-100 × 10^9/L, n (%)	1 (1)	59 (2.6)	
Platelets 100-150 × 10^9/L, n (%)	5 (5)	285 (12.5)	
Platelets >150 × 10^9/L, n (%)	82 (82)	1870 (82.3)	
Creatinine, median (IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0 (−0.1 to 0.1)
CrCl<30 mL/min, n (%)	2 (2)	55 (2.4)	
CrCl 30–50 mL/min, n (%)	8 (8)	169 (7.5)	
CrCl 51–80 mL/min, n (%)	37 (37)	608 (26.8)	
CrCl >80 mL/min, n (%)	53 (53)	1433 (63.3)	
Reasons for delay			
Referral for expertise, n (%)		38 (38)	
Thrombocytopenia, n (%)		10 (10)	
Active or recent bleeding, n (%)		12 (12)	
Recent or planned surgery, n (%)		16 (16)	
Patient choice, n (%)		4 (4)	
Missed diagnosis, *n* (%)		7 (7)	
Logistics, *n* (%)		6 (6)	
Not available, *n* (%)		7 (7)	

Note: For subjects included, <1% were missing the above demographic data for weight, sex, provocation, and baseline laboratory tests.

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]For incidental versus symptomatic pulmonary embolism, n = 1248. Information was missing in 1 of 37 patients with delayed anticoagulation and in 3 of 1211 with nondelayed anticoagulation.; [b]Percentage of patients with cancer receiving chemotherapy; n = 65 in the delayed group and n = 1095 in the nondelayed group.

TABLE 2 Comparison of clinical outcomes between patients with delays in anticoagulation therapy versus patients without delay reported by outcome rate per 100 person-years

Outcome	Delay (95% CI)	No delay (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
VTE recurrence	8.77 (4.08-18.32)	3.80 (3.03-4.75)	2.12[1] (0.92-4.89)	1.83[a] (0.78-4.32)
Major bleed	11.32 (5.89-21.73)	4.67 (3.81-5.72)	2.20[1] (1.07-4.54)	1.82[a] (0.89-3.74)
Clinically relevant nonmajor bleed	9.96 (4.93-20.11)	6.31 (5.30-7.51)	1.45[1] (0.68-3.12)	1.40[a] (0.65-3.01)
All-cause mortality	57.56 (47.37-69.93)	31.33 (29.34-33.44)	1.94 (1.42-2.64)	1.55 (1.14-2.11)

Abbreviations: CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

[a]Fine and Gray used to compare accounting for death as a competing risk.

in the subsequent 24 to 48 hours from diagnosis. In all events, anticoagulation was initiated appropriately following the procedure according to current recommendations. Our study categorized thrombocytopenia as the cause of delay when it was the documented rationale from the treating provider, not based on discrete lab values. It is likely that the high incidence of malignancy in our study population corresponded with the high prevalence of bleeding risk and thrombocytopenia.[21,22] Our study population was too small to draw further conclusions on optimal timing or dosing of anticoagulation in this subset of patients.

4.1 | Clinical outcomes

The small number of cases with delayed initiation of therapy limited our ability to compare the clinical profile of this patient group and analyze clinical outcomes compared to the majority of those with prompt anticoagulation initiation. Initial comparison between the anticoagulation-delay and prompt-anticoagulation groups revealed a significant difference in death and major bleeding at 90 days; however, the difference did not remain significant after adjustment for age, weight, and malignancy status. The incidence of CRNMB events and VTE recurrence were not statistically different between the groups at 90 days. After adjustment, HR remained elevated for VTE recurrence and major bleeding events, which could suggest an association with anticoagulation delay; however, further studies with higher power are needed to validate this. We could not confirm that the higher mortality in the anticoagulation-delay group is related to the delay in anticoagulation itself or signals the higher risk profile of patients in this subgroup. As stated, one contributor was likely the higher frequency of malignancy in the anticoagulation-delay group, conferring elevated rates of thrombocytopenia, bleeding risk, recurrent VTE events, and need for additional surgeries to address malignancy.[5,21]

A limitation to our study was that the results may not be representative of other practice systems. We were aware that our practice, being a specialty clinic at a quaternary center, may have significantly different results when compared to other institutions. Our system included a highly accessible anticoagulation clinic allowing for same-day appointments, 24/7 inpatient coverage, and a dedicated physician on call to guide outpatient therapy. Incorporation of patient-specific costs with an on-site pharmacy and on-site nursing education all increase the likelihood of prompt initiation. It is difficult to determine if findings would be similar in all settings or if alternative barriers exist. Additional limitations of our study included a relatively small population size for which treatment was delayed at our institution, statistically increasing the risk for type II error, particularly when comparing clinical outcomes.

5 | CONCLUSION

In summary, the results of our study suggested that delays in time to treatment with anticoagulants in this organized system of patient referral and follow-up are uncommon but also mostly modifiable. Delays in therapy due to pending expert referral for cancer-associated VTE and VTE of atypical location suggest the need for further clarification on treatment guidelines to minimize delays, particularly in regions without access to specialty referral. Additionally, while infrequent, the anticoagulation delay caused by logistics and missed diagnosis represents a potential patient safety hazard and highlights the need for a cohesive electronic medical record across hospital systems to minimize errors and missed opportunities. While we could only reflect on the preventable etiologies of anticoagulation delay in our center, we suggest other centers consider a review of anticoagulation-delay events to aid in determining global causes of delay, with hopes of improving patient care and outcomes.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

N.E.B. contributed to the design of the study and data acquisition, drafted the first version of the manuscript, and revised the manuscript critically for important intellectual content. WEW designed the study and provided methodological input, and revised the manuscript critically for important intellectual content. DOH performed the analyses and drafted the first version of the manuscript and revised the manuscript critically for important intellectual content. DTV contributed to the design of the study, data acquisition, and data verification; and revised the manuscript critically for important intellectual content. DEH contributed to the design of the study, data acquisition, and data verification; and revised the manuscript

critically for important intellectual content. AIC designed the study and provided methodological input, and revised the manuscript critically for important intellectual content.

ORCID

Nichole E. Brunton https://orcid.org/0000-0002-1867-6768
Waldemar E. Wysokinski https://orcid.org/0000-0002-8119-6206
Danielle T. Vlazny https://orcid.org/0000-0001-7074-6391
Damon E. Houghton https://orcid.org/0000-0002-6065-9523
Ana I. Casanegra https://orcid.org/0000-0001-6114-4284

TWITTER

Nichole E. Brunton @NicholeBrunton

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