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Asymptomatic "breakthrough" thrombosis and anticoagulant "failure": Keep calm and carry on

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Abstract

Despite therapeutic anticoagulation, patients with venous thromboembolism (VTE) not uncommonly present with findings of progressive thrombosis, sometimes within the first several weeks of treatment. While the prevailing strategy in these scenarios is to assume the current anticoagulant is ineffective and to switch to a different drug class, this practice may be unnecessary. Numerous trials of heparins and vitamin K antagonists for VTE have demonstrated that asymptomatic thrombus propagation despite therapeutic anticoagulation is common. While similar, serial imaging studies after initial VTE have not been replicated in trials of the direct oral anticoagulants, we reason that asymptomatic thrombus propagation detected within the first month of VTE diagnosis can be managed with continuation of the current anticoagulant strategy and close follow-up for worsening or recurrent symptoms.

KEYWORDS

anticoagulant, heparin, postthrombotic syndrome, thrombosis, venous thromboembolism

Therapeutic anticoagulation effectively prevents recurrent thrombosis for a majority of patients with venous thromboembolism (VTE), with recurrence rates of approximately 2% using the direct oral anticoagulants (DOACs).[1] Yet the possibility of VTE recurrence, often colloquially referred to as "breakthrough thrombosis" or "anticoagulant failure," creates anxiety for patients and providers and remains a clinical dilemma for multiple reasons, including a lack of consistent radiographic criteria for diagnosing recurrent VTE, poor correlation between persistent or recurrent VTE symptoms and true breakthrough thrombosis, and the lack of validated "therapeutic" plasma DOAC drug levels to prove appropriate DOAC dosing.[2,3] But might our commonly held definitions of breakthrough misrepresent a natural physiologic process? Interestingly, abundant data from early studies of heparin and vitamin K antagonists (VKAs) that employed serial imaging reveal a relatively high rate of asymptomatic thrombus propagation early in the course of VTE treatment. Herein, we synthesize this literature and submit that incidentally detected, *asymptomatic* thrombus propagation within 30 days of initial VTE should not be interpreted as breakthrough or anticoagulation failure. Rather, these patients can be safely monitored for new or worsening symptoms with continuation of their current therapy.

Unlike modern trials, many early studies of heparins and VKAs for acute VTE management performed serial imaging after the initial VTE diagnosis to screen for asymptomatic thrombus propagation. After initiating therapeutic anticoagulation, repeat imaging studies (typically contrast venography or compression ultrasonography with Doppler) were repeated at various intervals. Descriptions of select studies of deep vein thrombosis (DVT) treatment and asymptomatic thrombus propagation rates are shown in Table **1**. Collectively, these studies reveal that despite therapeutic anticoagulation, DVT propagation can be detected in a substantial proportion of patients. In multiple single-arm cohort studies, propagation occurred in 10% to 38% of patients within

TABLE 1 Details of studies reporting screened thrombus propagation rates and timing

Study	Patients (n)	VTE cause	Treatment(s)	Follow-up imaging	Criteria for clot propagation	Incidence and timing of clot propagation	Comments
Killewich et al 1989[4] Single-arm observational study	21	All provoked	Therapeutic i.v. UFH or VKA	Venous duplex US on days 7, 30, 90, 180, and 270.	Increase in number of totally occluded venous segments	3/21 (14%) within 7 d 4/21 (19%) within 30-180 d	
Krupski et al 1990[5] Single arm observational study	24	Provoked: 16 (3 patients with cancer) Unprovoked: 8	Therapeutic i.v. UFH, bridged to VKA	Venous duplex US "on average every 2 d" (mean 2.2 ± 1.1) for 4 total scans per patient	Thrombus in a more proximal venous level than at initial diagnosis.	9/24 (38%). 6 within 3 d, 2 additional within 5 d, 1 additional within 7 d	~33% of patients in both arms inadequately anticoagulated (APTT < 1.5× baseline while on UFH)
Thomas et al 1971[6] Single-arm observational study	21	Not described	Some on anticoagulation, but numbers not described	Venography on days 3-12	New venous occlusion, thrombus adherence or retraction	3/10 (30%) within 3-12 d	Unclear how many patients with propagation were on anticoagulation
Van Ramshorst et al 1992[7] Single-arm observational study	18 (80 vein segments)	Provoked: 11 Unprovoked: 7	Therapeutic i.v. UFH, bridged to VKA	Venous duplex US at 1, 3, 6,12, 26 wk	Numerical thrombosis score: 0 = patent, 1 = non-occlusive, 2 = occlusive	5/18 (27.8%) within 1 wk 2/18 (11.1%) within 1-3 wk 1/18 (5.5%) within 3-6 wk 3/18 (16.6%) within 6-12 wk 4/18 (22.2%) within 12-26 wk	
Caprini et al 1995[8] Nonrandomized cohort study	69	Not described	Therapeutic i.v. UFH or VKA	Venous duplex US at 1, 4, 12, 24 wk	New vein segment involved by thrombus	0%-5% within 1 wk	Adequacy of anticoagulation unclear, and rates of propagation in individual treatment cohorts not described
Meissner et al 1995[9] Single-arm observational study	177 (204 limbs)	Provoked: 148 (33% with cancer) Unprovoked: 29	Therapeutic i.v. UFH or VKA (65%-88.9% of patients on 1 or both at time of clot propagation)	Venous duplex US at days 1 and 7, 1 mo, every 3 mo for 1 y, then annually	Patent, partially occluded, or completely occluded, and location classified as propagation, rethrombosis or contralateral limb involvement	61/204 (30%), median 9-39 d	Unclear what proportion of those with clot propagation were on anticoagulation at time of event

(Continues)

the first 14 days of treatment despite therapeutic anticoagulation.[4–9] Several RCTs comparing unfractionated heparin (UFH) to low-molecular-weight heparin (LMWH) also occasionally included serial screening imaging studies and found propagation rates ranging from 1.1% to 15%, again within the first 10 to 14 days of therapy.[10–12] Finally, some randomized controlled trials (RCTs) comparing UFH to LMWH in which repeat imaging was triggered only for new or progressive symptoms reported patient-level data on the timing of recurrent

TABLE 1 (Continued)

Study	Patients (n)	VTE cause	Treatment(s)	Follow-up imaging	Criteria for clot propagation	Incidence and timing of clot propagation	Comments
Prandoni et al 1992[10] Randomized controlled trial	170	Provoked: 104 (33 [19%] with cancer) Unprovoked: 66	Therapeutic i.v. UFH or LMWH, bridged to VKA	Venography on day 10; sooner if symptoms. If venogram inconclusive: radiolabeled fibrinogen scan	Quantitative venography score, with recurrence defined as new intraluminal filling defect on venogram or fibrinogen scan	UFH: 4/85 (4.7%) within 10 d LMWH: 1/85 (1.1%) within 10 d	2 of 4 recurrences in UFH group due to HIT
Walker et al 1987[11] Randomized controlled trial	100	Provoked: 87 Unprovoked: 13	Subcutaneous UFH or therapeutic i.v. UFH	Venography "after completion of treatment" (maximum 14 d)	Not described	IV UFH: 13/47 (27.7%) within 14 d Subcutaneous UFH: 2/49 (4.1%) within 14 d	
Simonneau et al 1993[12] Randomized controlled trial	134	Provoked: 44 (9 (6.7%) with cancer) Unprovoked: 90	Therapeutic i.v. UFH or LMWH, bridged to VKA	Venography on day 10, or sooner if symptomatic	Proximal propagation of at least 1 cm	UFH: 7/67 (10.4%) within first 10 d LMWH: 1/67 (1.5%) within first 10 d	
Kearon et al 2006[13] Randomized controlled trial	708	17% with cancer Other details not available	Fixed-dose UFH vs. LMWH, bridged to VKA	Venography or venous duplex US for symptoms	New vein segment involvement	UFH: 1 (0.3%) within first 10 d, 13 (3.8%) within 3 mo LMWH: 2 (0.6%) within first 10 d, 12 (3.4%) within 3 mo	20%-23% of INR values <2.0 in both study arms
Prandoni et al 2004[14] Randomized controlled trial	720	Provoked: 533 (22% with cancer) Unprovoked: 155	Therapeutic i.v. UFH or LMWH, bridged to VKA	Venography or venous duplex US for symptoms	New intraluminal filling defect on venography, or new vein segment involvement or substantial increase in thrombus diameter on US	UFH: 5 within 2 wk, 4 within first 30 d, 6 in in remaining 6 wk (4.2% total) LMWH: 4 within 2 wk, 5 within first 30 d, 5 in remaining 6 wk (3.9% total)	Only 73% of subjects reached therapeutic aPTT threshold within 24 h in UFH group 30% of INR values <2.0 in both arms

APTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; i.v., intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; US, ultrasound; VKA, vitamin K antagonist.

thrombotic events; 2 such studies included a total of 1428 patients and found symptomatic thrombus propagation rates from 0.3% to 4.2% within the first 6 weeks of anticoagulation.[13,14] Perhaps reflecting these propagation rates, a state-of-the-art ultrasound guideline in 1993 stressed the "dubious" role of serial imaging in patients with anticoagulant-treated DVT.[15] Similarly, the Society for Vascular Medicine's "Choosing Wisely" guidelines recommend against serial imaging of established DVT in the absence of worsening symptoms.

These results must be interpreted in the context of significant heterogeneity in study execution, including variable subject inclusion criteria; lack of information on concurrent use of antiplatelet medications; and inconsistent anticoagulant dosing, imaging modalities utilized, and criteria to define worsening thrombosis. Confounding factors affecting detectable VTE progression should also be considered: In several studies, patients were below the therapeutic range of either heparin or VKAs for up to a third of the study time.[5,13]

Along these lines, the activated partial thromboplastin time (APTT), though often used in these studies, has largely been replaced by the anti-Xa assay for measuring blood levels of heparin products given its superior sensitivity and specificity. The incidence or prevalence of significant acquired VTE risk factors such as heparin-induced thrombocytopenia and cancer were inconsistently reported. Finally, despite the use of compression ultrasound with Doppler to diagnose VTE similar to modern medical practice, rates of false positives in these early studies may have been higher simply due to different operator technique or inferior technology.

Despite these points, the results of these studies are compelling, in aggregate demonstrating nonnegligible rates of early, asymptomatic thrombus propagation as high as 30% despite therapeutic anticoagulation. While thrombus propagation is most often diagnosed due to new patient symptoms, our group has encountered numerous cases in which imaging studies performed for unrelated reasons detected extension of previously diagnosed thrombosis, and thus we feel this phenomenon merits discussion of several important questions. First, might thrombus propagation simply be a misinterpretation of the natural history of VTE? It must be emphasized that VTE is not an event, but rather a prolonged inflammatory process, with the initial thrombus and associated vein segments undergoing dynamic processes of remodeling and fibrosis driven in large part by inflammatory cytokines.[7,16] Anticoagulation therefore targets only one of many facets of VTE pathophysiology, and changes in thrombus appearance, whether true growth in size or fibrosis and contraction mimicking growth, should be expected in the early phase of disease. Indeed, it is recognized that scarring of the vessel wall and turbulent blood flow after DVT can be difficult to differentiate from fresh thrombus, potentially leading to false positives.[3] The natural history of untreated DVT would serve as a useful comparison, though such data are limited; for untreated, isolated, distal lower extremity VTE followed with serial imaging, a systematic review described a proximal propagation rate of 10%.[17] Acknowledging the risks of cross-trial comparisons, this rate falls within the range of propagation rates discussed above for treated patients.

Second, it remains unclear whether asymptomatic thrombus propagation represents a clinically relevant entity distinct from symptomatic breakthrough (eg leading to higher rates of postthrombotic syndrome [PTS] or mortality). Long-term outcomes of the discussed studies were inconsistently reported, and no randomized trials exist to directly answer this question. Persistent VTE symptoms at 1 month and residual thrombosis at 3 to 6 months have been identified as having modest association with development of PTS[2] similarly robust data are lacking on such an association with asymptomatic thrombus propagation, although a study by Meissner et al[9] found significantly higher rates of venous reflux in patients experiencing early rethrombosis.

Third, it is unclear whether the rates of early, asymptomatic DVT propagation can be extrapolated to cases of pulmonary embolism (PE). Importantly, the majority of studies listed in Table 1 described patients with DVT only. While the pathophysiologic concepts of inflammation and thrombus remodeling discussed above could reasonably apply to multiple forms of venous thrombosis, data for asymptomatic PE propagation is less abundant and beyond the scope of this discussion. Similarly, it also remains unclear whether asymptomatic thrombus propagation seen with heparins and VKA should also be expected with DOACs. Modern trials leading to DOAC approvals have reported only aggregate, symptomatic VTE recurrence without patient-level outcomes, and thus early propagation rates with DOACs remain largely unknown. The noninferiority, and in some cases superiority, of DOACs compared to heparins and VKAs for VTE treatment reported in major trials, however, makes it unlikely that thrombus propagation rates would be higher with DOACs.[1]

Finally, the precise time at which thrombus propagation is no longer expected remains to be clarified. Guidelines from the ISTH suggest criteria for diagnosing recurrent DVT, including elevated D-dimer measurements and a difference in residual vein diameter >4 mm between serial ultrasound images, though these guidelines do not define *when* such findings justify treatment changes.[18] We reason that based on available data, a cutoff of ~30 days would seem reasonable, and that *asymptomatic* thrombus propagation diagnosed within this time frame can be ignored with no changes in anticoagulant therapy. However, a practice of close clinical follow-up and heightened patient vigilance for symptoms of worsening DVT should be followed. We do not recommend serial imaging to monitor for further progression in the absence of symptoms; while this practice is advised for some cases of untreated superficial and distal lower extremity venous thrombosis, with initiation of anticoagulation if thrombus propagates closer to the proximal deep veins, evidence is lacking for the same strategy in cases of *treated* proximal DVT with asymptomatic progression.[19] As data on outcomes of *symptomatic* DVT progression without changes in anticoagulant therapy are scarce, we feel that these cases cannot be dismissed and that switching to an alternative anticoagulant should be strongly considered, as recommended in a recent review by Schulman et al.[20]

Several potential strategies for future research could help address knowledge gaps in the management of thrombosis progression or breakthrough. First, it would be helpful to know the rates of asymptomatic VTE propagation in patients treated with DOACs, which should consist of frequent screening imaging in a prospective randomized or cohort VTE treatment trial. This study outcome should also be applied to patients treated specifically for PE, to clarify whether this form of venous thrombosis should be considered distinct. In conjunction, prospectively tracking clinically relevant long-term outcomes of asymptomatic thrombus propagation, including development of PTS, recurrent VTE, and mortality would also help to clarify the true clinical significance of this entity. Also aiding in the distinction between symptomatic and asymptomatic thrombus propagation could be a change in the naming conventions of these entities, such that “breakthrough” refers only to symptomatic or late (>30 days) propagation. Ultimately, these strategies could help to further narrow our definitions of “breakthrough” or anticoagulation “failure,” helping medical providers avoid unnecessary changes in therapy and reducing both provider and patient anxiety.

RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

SO: data collection and review, manuscript composition; JS: critical edits. TD: critical edits, project conception.

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