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Review Article

Management of suspected and confirmed recurrent venous thrombosis while on anticoagulant therapy. What next?

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ABSTRACT

Suspected recurrent venous thromboembolism (VTE) is a common and vexing clinical problem. Confounding the diagnosis of recurrent VTE is a high frequency of residual VTE from prior VTE. The diagnosis of recurrent VTE must be established by comparing current imaging with past imaging to distinguish acute from chronic thrombosis. Next, we must ascertain if non-compliance was the cause of "apparent therapeutic failure" and if non-compliance is at play then re-initiate anticoagulant therapy. Therapeutic failure is relatively uncommon. As such, we must consider underlying causes of therapeutic failures including malignancy and potent thrombophilias. Finally, short term anticoagulant management of therapeutic failures is controversial, and requires further research, but the best current evidence supports a course of full-dose low-molecular-weight heparin (LMWH) (and dose escalated LMWH if failure occurs while on full-dose LMWH).

1. Introduction

Case: John Smith is on anticoagulant therapy for prior unprovoked DVT and PE and presents with 2 days of new leg pain and leg swelling and vague complaints of dyspnea. The emergency physician has done a leg vein ultrasound which has been reported as "likely acute on chronic thrombosis in the femoral vein". Next the emergency physician orders a CT pulmonary angiogram which reports a "right upper lobe filling defect". John is on Vitamin K antagonists (VKA) with an INR of 1.9. How do we manage this patient?

First and foremost, we must acknowledge that the management of recurrent venous thromboembolism (VTE) on anticoagulants or "therapeutic failure" is an "evidence-poor zone". In this paper we will review the limited evidence to guide us in managing Mr. Smith and at the same time we will provide our approach to the management of these patients. Only further research and time will tell if our approach is safe and effective.

2. Management of suspected and confirmed therapeutic failure

It is important that "suspected treatment failure" be "confirmed treatment failure" and not mis-diagnosis of recurrent VTE or due to non-compliance (i.e. not true treatment failure). Falsely labelling a patient as having treatment failure leads to worry about underlying serious diagnoses (see below) and leads to an unnecessary escalation in anticoagulant therapy.

Here are the steps we follow in managing patients with apparent "treatment failure" (see Fig. 1).

1. Confirm the diagnosis of recurrent venous thromboembolism

It bears emphasis that many apparent "treatment failure" presentations are in fact residual venous disease masquerading as recurrent VTE.

For the purposes of this paper we will classify "index" venous thrombosis imaging as imaging that occurs at the time of first symptomatic acute VTE. We will refer to "baseline" imaging as imaging that is completed after a minimum of three months of anticoagulant therapy (i.e. post initial anticoagulant therapy).

2.1. How frequent is residual venous disease?

Cohort studies with serial imaging of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) demonstrate how often residual venous disease will persist on imaging. In the REVERSE study, 646 patients with unprovoked VTE had "baseline" leg vein imaging and/or ventilation/perfusion scan (V/Q) 5–7 months after index DVT and/or PE [1]. Baseline imaging was abnormal in 60.5% (391/646) of patients.

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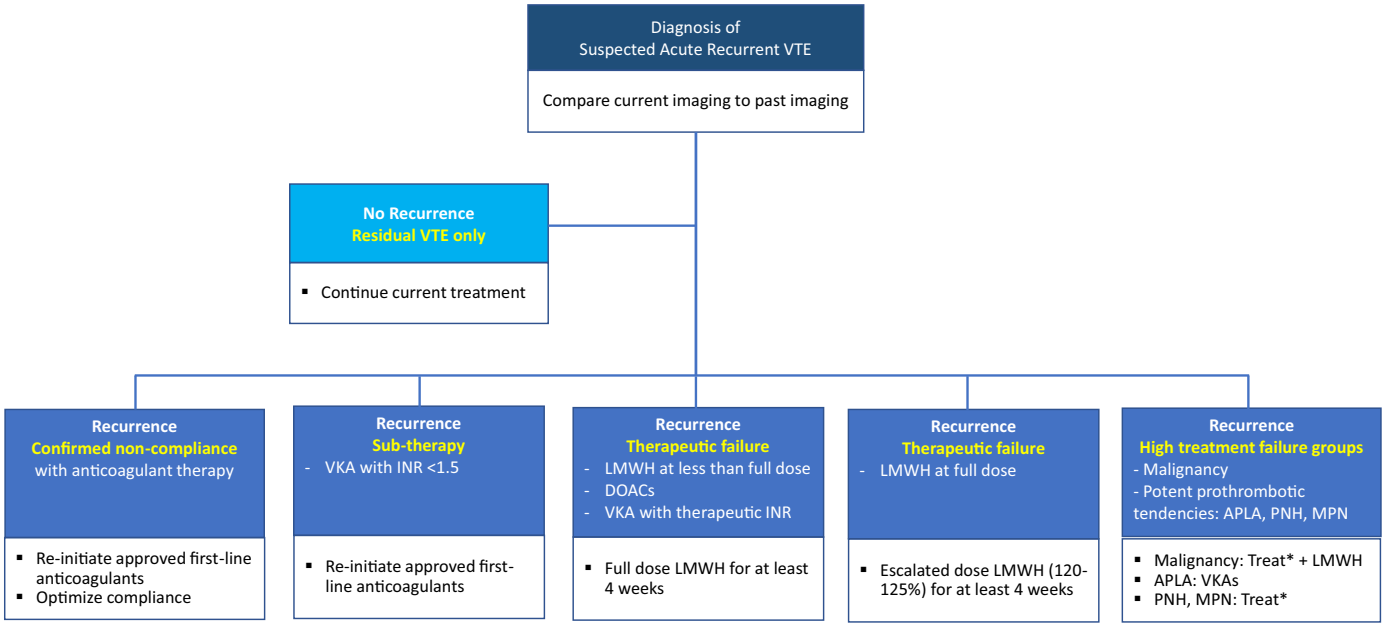

Fig. 1.

In an individual patient data meta-analysis of 2527 patients with unprovoked DVT from 10 prospective cohort studies, 55.1% (1380/2527) of patients had residual venous obstruction a median of six months after their index DVT [2]. Similarly, a systematic review of studies exploring residual PE on V/Q or CT pulmonary angiography (CTPA) imaging, identified abnormalities on follow-up imaging in over 50% of PE patients 6–11 months after index PE [3]. In contrast, in a cohort study of PE patients with baseline CTPA at 6 months, Den Exter et al. demonstrated that most patients have complete resolution on CTPA (> 84%) arguing against performing baseline CTPA. There is less radiation exposure with baseline VQ scan than baseline CTPA favoring doing baseline VQ scans. Furthermore, having a baseline V/Q scan permits VQ scans to be conducted with subsequent suspected recurrent PE further reducing radiation exposure [4]. Also, many patients have findings of chronic thromboembolic pulmonary hypertension on the initial CTPA diagnosing their initial PE suggesting prior undiagnosed PE [5]. Overall, it should not be surprising that many patients, indeed over 50% of patients, with suspected recurrent VTE will have residual venous disease from the index event potentially confounding the diagnosis of a recurrent event.

2.2. How frequently do patients with prior VTE present with signs of recurrent VTE?

It is very common for patients with prior VTE to present with suspected recurrent VTE. Indeed, in the REVERSE study, over a mean follow-up of 5 years off of anticoagulant therapy after unprovoked VTE, 663 suspected recurrent VTE were investigated in 62% of study patients (408 patients had suspected VTE/663 total patients) and only 40% of these suspected events were confirmed (165 confirmed recurrent VTE/408 patients suspected to have recurrent VTE) [6]. This should not be surprising given how common leg swelling and discomfort are after DVT [7] and how commonly patients have residual dyspnea after PE [8].

2.3. Can imaging tests distinguish acute vs chronic residual VTE?

The radiology literature is rife with poorly supported claims that certain characteristics on ultrasound imaging of DVT or CT imaging of PE can help us to distinguish between acute and chronic VTE. These distinguishing characteristics include the presence of collateral vessels, partial venous compressibility of chronic thrombus, venous/arterial vessel distension by acute thrombosis, calcification of chronic thrombus, higher density of chronic thrombus and use of acute angles between thrombus and the vessel wall to support diagnosis of acute thrombosis [9,10]. Indeed, no formal management studies have been published to support the safety of withholding anticoagulants in patients with suspected recurrent events and a diagnostic imaging characteristic that supports chronic thrombosis using any of these criteria. Promising works using magnetic resonance direct thrombus imaging (MRDTI) to differentiate old vs new thrombus is underway but management studies will be required before MRDTI is ready for use in clinical practice (NCT02262052).

2.4. Can D-Dimer testing help differentiate acute vs. chronic disease?

Studies exploring the use of D-Dimer alone or in combination with clinical pre-test probability assessment are limited for patients presenting with suspected recurrent VTE [11]. Early results are reassuring but not yet definitive (point estimates of the risk of recurrent VTE in those with negative D-Dimer look promising but upper bounds of 95% confidence intervals (CI) are higher than accepted standards). Hence, for now, we are left with relying on diagnostic imaging approaches to conclusively diagnose or exclude recurrent VTE.

2.5. Can baseline imaging help differentiate acute vs. chronic disease?

Le Gal and colleagues have shown that a diagnostic strategy based on comparing imaging at the time of suspected recurrent VTE to baseline imaging can be safely used to exclude recurrent VTE. In this study, 8 of 284 patients in whom VTE was excluded with this strategy and had anticoagulants withheld, had recurrent VTE over 3-month follow-up. Furthermore, 6 of these 8 “diagnostic failures” had superficial thrombosis or distal DVT at the time of suspected recurrent VTE suggesting that this strategy would be even safer in those without distal DVT or superficial thrombosis (failure rate of 0.7% (2/284), 95% CI 0.2–2.5%) [12]. Similarly, Hamada and colleagues demonstrated that in the absence of baseline imaging, the proportion of patients that are “classifiable” by expert adjudicators at the time of suspected recurrent VTE diminishes from over 95% with baseline imaging to approximately

80% in the absence of baseline imaging [13]. That is, 1 in 6 suspected recurrent VTE become "not classifiable" in the absence of baseline imaging. Overall, given the high stakes nature of the decision to label a patient as having recurrent VTE, it is essential that efforts are made to retrieve index and baseline VTE imaging and compare it to current imaging in order to make the right diagnosis. A thrombus that is present in an area not involved at the time of the index VTE can be labelled as a recurrent event. Also, an area of thrombosis not involved at the time of baseline imaging can be labelled as recurrent VTE.

While it may not ultimately prove to be cost effective to conduct universal baseline imaging after treatment in all VTE patients, we advocate for baseline imaging in patients with a high risk of recurrent VTE. These include patients who are recommended to discontinue anticoagulants, are likely to discontinue anticoagulants despite recommendations to continue anticoagulants or at high risk of on-treatment failure.

Returning to our case, we needed to obtain the leg vein and pulmonary artery imaging reports from the time of John's index event and any subsequent imaging in order to correctly ascertain whether John's current imaging abnormalities are indeed recurrent VTE or residual venous disease from his index event. It turns out that John's prior DVT was in his other leg (i.e. not the currently symptomatic leg) and that he had a baseline V/Q scan 6 months after his index PE that was normal so we can be certain that he indeed had a recurrent DVT and PE while on a VKA.

2. Consider the etiology of recurrent VTE on anticoagulants

Recurrent VTE while on anticoagulant therapy is an unusual enough event that a search for a cause of the recurrent event is probably warranted. In a meta-analysis of 26,872 VTE patients in modern acute VTE treatment trials (most treated for 6 months with one trial permitting treatment up to 1 year), van Es and colleagues showed that the risk of recurrent VTE during the acute treatment phase was ~2% in DOAC and vitamin K antagonist (VKA) treated patients [14]. Also, in a long-term secondary prevention network meta-analysis Wang and colleagues calculated a pooled event rate of 1.2 per 100 person years with standard intensity VKA with comparable rates using other anticoagulant options [15]. Hence, the large majority of patients in the acute, sub-acute and long-term VTE treatment phases do not develop recurrent VTE, which in turn behooves us to ask **why** patients develop recurrent VTE.

The answer to **why** a patient develops recurrent VTE might include the following:

1) Non-compliance- Given the high rates of recurrent VTE in patients in whom ongoing anticoagulation for secondary VTE prevention is warranted but not continued and the high relative risk reductions (> 80%) with adequate anticoagulation [14,15], it should not be surprising to find that non-compliance is likely a key etiology of "apparent treatment failure". Compliance with VKA is easy to measure and document with an INR at the time of the recurrent VTE. More challenging is the ability to measure and document non-compliance with direct oral anticoagulants (DOACs) given the absence of widely available tests, absence of validated tests and expected therapeutic ranges for these tests. Nonetheless, if a patient claims to have taken a DOAC in the last 12–24 h and has a normal anti-Xa measurement (for rivaroxaban, apixaban or edoxaban) or a thrombin time (for dabigatran), then it is highly likely they were non-compliant. Some literature supports that non-compliance with DOACs is common. In atrial fibrillation patients, rates of persistence with DOAC therapy are < 50% at 1 year [16]. Early studies suggest non-adherence is also a significant issue in VTE patients [17]. Given the relatively short half-lives of the DOACs, DOAC non-compliance may have even greater consequence in VTE than Vitamin K antagonist non-compliance as missing as few as 1–2 DOAC doses may result in no effective residual anticoagulant activity within 24–48 h.

   We look forward to sub-group analyses of DOAC RCTs in VTE treatment exploring the relative effectiveness of DOACs in non-compliant or poorly compliant populations.

   If a patient is found to have been non-compliant at the time of "apparent therapeutic failure" they should be managed with the same anticoagulant therapeutic approaches and doses as patients with a first VTE.

   Next, efforts to optimize compliance are required to prevent a subsequent recurrence. These efforts should focus on the individual reasons for non-compliance (memory issues, affordability etc.). Compliance aids can be offered to those who forget to take their pills including pill boxes, smartphone applications with automated reminders etc.

   A point of contention and subtlety is what INR threshold to use to declare sub-therapy as the etiology of recurrent VTE and to then suggest a more intensive anticoagulant approach if this INR threshold is not met (see below). Some authors have suggested an INR of < 1.9 should define the threshold where sub-therapy can be blamed and where a more intensive anticoagulant approach is then warranted [18]. However, given that low intensity VKAs (INR 1.5–2.0) appears to be almost as effective as usual intensity VKAs (INR 2.0–3.0) [19], a stronger rationale is to use an INR < 1.5 as the INR threshold for sub-therapy.

2) Underlying cancer- In patients with cancer-associated thrombosis, therapeutic failures are more common. Prandoni and colleagues have shown that cancer patients have a 3–4 fold higher risk of recurrent VTE compared to non-cancer patients [20]. More recent studies corroborate these high rates of treatment failure in cancer-associated thrombosis. In the CLOT study, Lee and colleagues demonstrated that over 15% of patients on VKAs and over 8% of those on dalteparin developed recurrent VTE during the initial 6 months of anticoagulant therapy [21]. More recently, Li and colleagues showed in a meta-analysis of DOAC for cancer-associated thrombosis studies that over 5% of cancer patients develop recurrent VTE during the initial 6 months of anticoagulant therapy [22].

   In patients without documented cancer, clinicians/patients/policy-makers may question whether a search for underlying occult cancer is warranted in those with therapeutic failure. Indeed, Rezig and colleagues recently showed that the incidence of occult cancer detection in patients with a second episode of unprovoked VTE while on anticoagulant therapy was very high with a rate of 35.8% (95% CI, 19.7–59.2%) [23]. These high rates suggest that clinicians should have a low threshold for occult cancer screening and start with history, physical and simple age appropriate screening tests to start, followed by more costly tests such as CT chest, abdomen and pelvis [24]. It should be noted that detection of underlying cancer will not necessarily improve survival.

3) Anti-phospholipid antibody (APLA) syndrome- Schulman and colleagues showed that the risk of recurrent VTE off of anticoagulant therapy at 4 years was 29% (20/68) in patients with anticardiolipin antibodies and 14% (47/334) in patients without antibodies ((p = 0.0013; Risk ratio: 2.1 (95% CI 1.3 to 3.3)) [25]. There is little literature to document the rate of treatment failure in APLA patients [26]. However, a recent RCT comparing rivaroxaban to standard intensity VKA in triple positive APLA patients demonstrated a high risk of recurrent VTE. Over a mean follow-up of ~18 months, there were 11 (19%) venous and arterial events in the rivaroxaban group and 2 (3%) in the VKA group [27]. These findings not only suggest better efficacy with VKAs but also suggest a high rate of treatment failure in APLA patients such that a search for triple positive APLA is strongly suggested in patients who experience anticoagulant treatment failures. If triple positive APLA is confirmed then VKAs should be the preferred long-term anticoagulant management option

pending further research with alternative anticoagulant management approaches.

4) Other potent prothrombotic tendencies- In patients taking heparin or low-molecular-weight heparin (LMWH) who develop treatment failure, a consideration for heparin induced thrombocytopenia (HIT) is warranted given a high rate of thrombosis if heparin/LMWH are not discontinued. Patients with paroxysmal nocturnal hemoglobinuria (PNH) and myeloproliferative disease (MPN) also likely have higher risks of recurrent VTE on treatment and have specific therapies that may be initiated to reduce the risk of recurrent VTE. These conditions may be apparent or suggested on a simple complete blood count (CBC) and LDH. Whether to test for PNH or MPNs in patients with therapeutic failure is more controversial. Recently, Ianotto and colleagues showed in a prospective cohort study of VTE patients that among 19 patients who developed recurrent VTE on therapy 4 had the JAK2V617F mutation, suggesting that patients with therapeutic failure should potentially be tested for the JAK2V617F mutation so that they may be more closely followed for the development of MPNs [28]. Finally, there is a poverty of literature on the frequency of "potent" inherited thrombophilia (e.g. antithrombin deficiency, double hits (e.g. double heterozygotes for Factor V Leiden and Prothrombin Gene Variant)) in patients with therapeutic failure and the therapeutic management of therapeutic failure in these patients.

Case- Returning to our patient, John's INR was 1.9 confirming that he was compliant with his VKA. He was up to date with age/gender appropriate occult cancer screening and review of systems, examination and lab tests did not suggest the need for further investigations for underlying malignancy. Complete thrombophilia panel was normal. His CBC and LDH were normal, reducing the likelihood of PNH or MPN. JAK2V617F testing was also normal. Overall, we were left without a clear reason for his therapeutic anticoagulant failure.

3. Therapeutic choices in patients with treatment failure

2.6. Very early "treatment failure" (< 1 week)

In patients who develop recurrent VTE early on in therapy (e.g. within the first week), there is little expectation that thrombus will have organized and endothelialized within this first week. As such these "fresh" thrombi may embolise despite anticoagulant therapy and not because of inadequacy of suppression of thrombin generation. As such, our approach is to maintain current anticoagulant therapy for very early new VTE. Nonetheless, this approach has never been prospectively validated and published but our local experience is reassuring.

2.7. Documented non-compliance

In patients who readily admit to having stopped their anticoagulants, who have no evidence of DOACs on board or whose INR is < 1.5, we suggest starting approved acute anticoagulant therapy at usual doses for treatment of a first acute VTE. Next, after a discussion to understand the reasons for non-compliance, targeted measures to improve compliance should be adopted (e.g. memory aids, pill boxes, sharing responsibility with a family member/close friend, measures to address affordability issues etc.).

2.8. Later treatment failure

The early therapeutic management of patients who fail full-dose VKAs, DOACs or full-dose LMWH is in the "evidence poor" zone. There are no randomized trials exploring different treatment options in patients with therapeutic failure of anticoagulation nor prospective cohort studies exploring uniform management strategies in these patients.

There are, however, compelling retrospective cohort studies that collectively provide some evidence, albeit weak, upon which to guide practice. Luk and colleagues reported a retrospective cohort study of 82 patients who developed recurrent VTE despite VKAs therapy, who were then switched to full-dose dalteparin for at least 4 weeks [29]. The risk of subsequent recurrent VTE was 9% (3/32; (95% CI 2–25%) over an unspecified duration of follow-up in these patients. Carrier and colleagues showed in a retrospective cohort study of 70 cancer patients that 1) patients who developed recurrent VTE on VKAs or less than therapeutic dose LMWH, who are then treated with full-dose LMWH for 4–12 weeks and 2) patients who developed recurrent VTE despite full-dose LMWH that are then treated with 120–125% full-dose LMWH for at least 4 weeks, have an 8.6% (6/70; 95% CI 4.0–17.5%) risk of recurrent VTE and a 4.3% (3/70; 95% CI 1.5–11.9%) risk of major bleed [30]. The same group showed similar results with this strategy in a non-overlapping retrospective cohort [31]. Finally, Schulman reported the results of an international registry of 212 patients with cancer who developed recurrent VTE on anticoagulant therapy then were subsequently managed with no change in therapy (i.e. same drug and anticoagulant intensity), switched to an alternative anticoagulant or dose escalated with the same therapy [32]. This study showed comparable findings to the aforementioned studies with an overall risk of recurrent VTE of 11% and a risk of major bleeding of 8%. In an interesting secondary analysis, the authors showed that those patients switched to LMWH had a lower risk of recurrent VTE than those who remained on VKAs (HR 0.28; 95% CI 0.11–0.70). Collectively, these studies suggest that LMWH (and dose escalated LMWH if failure occurs on full-dose LMWH) is a reasonable approach for confirmed treatment failure in cancer patients. Furthermore, there is no reason to believe that this strategy would not be effective in non-cancer patients given that cancer patients are generally at higher risk of recurrent VTE and bleeding (detailed above).

There are no published studies exploring options after DOAC failure. Options to explore in future research include dose escalated DOACs and switching DOACs. Until such studies are published, we suggest assuming the same approach as with patients who experience VKA failure (i.e. switch to full dose LMWH).

Inferior vena cava (IVC) filter use has been considered in patients with therapeutic failures and indeed in the past was recommended in guidelines [33]. However, given that IVC filters do nothing to suppress thrombin generation and provide a nidus of venous thrombosis, there is concern over their efficacy. In addition, RCTs of IVC filters in anticoagulated patients show no short or long-term survival benefit, overall no decrease in risk of PE and demonstrate an increase in DVT risk [34,35]. As such, current guidance recommends against the use of IVC filters in the management of therapeutic failure patients in the absence of contraindications to anticoagulation [36].

It is worth noting that there is little literature exploring the etiology and therapeutic management of patients with 2 or more therapeutic failures.

Case- John's therapeutic failure without clear underlying cause was managed with full dose LMWH for a month then he returned to Vitamin K antagonists with a target INR of 2–3 without any recurrent VTE over one-year follow-up.

3. Conclusion

In patients with suspected therapeutic failure, first and foremost confirm the diagnosis of recurrent VTE by comparing current imaging with past imaging (see Fig. 1). Next, ascertain if non-compliance was the cause of apparent therapeutic failure and if so re-initiate anticoagulant therapy and address the underlying reasons for non-compliance. Consider underlying causes of therapeutic failures including malignancy and potent thrombophilias. Finally, short term anticoagulant management of therapeutic failures is controversial, and requires further research, but the best current evidence supports a course

of full-dose LMWH (and dose escalated LMWH if failure occurs on full-dose LMWH).

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