

# Recurrent Venous Thrombosis and Breakthrough Thrombosis: A Narrative Review

Rasha A. Al-Khafaji\*

Department of Oncology, Centre for Cancer and Organ Diseases, Rigshospital, Copenhagen, Denmark

## Abstract

Venous Thromboembolism (VTE) is a vexing heterogeneous disease that, along with Myocardial Infarction (MI) and stroke, is among the top three cardiovascular killers. VTE's morbidity and mortality globally cause high social, health, and economic impacts. The modern diagnostic strategies of Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) developed to aid physicians in diagnosing these presentations and using imaging resources effectively have shown limitations in several subgroups, including patients with recurrent VTE or those who are already on anticoagulation therapy. In the light of a previously reported breakthrough (recurrent) DVT while on rivaroxaban 20 mg PO daily in a 43-year-old Caucasian female, this review discusses the various etiologies, which contribute to anticoagulant's failure and VTE's recurrences in general to increase awareness among practicing physicians about these subgroups. The roles of imaging and D-dimer testing in these subgroups are also discussed, leading the author to cautiously conclude that diagnostic imaging plays a central role in identifying recurrence regardless of D-dimer testing and recommending baseline sonography upon completing DVT anticoagulation therapy for future references. Accurate diagnostic strategies are needed to ensure the best available care and treatment reaches the patient. Based on this review, the author constructs a hypothetical algorithm targeted to diagnose recurrent VTE or breakthrough VTE while on anticoagulants coupled with the possible causes for recurrent and breakthrough VTE. This algorithm should only be considered as hypothesis-generating for specifically designed prospective studies to assess and validate the algorithm's potential in decreasing the incidence of missed diagnosis of VTE and their underlying etiologies in these subgroups.

**Keywords:** Anticoagulants failure • Autoimmune disease • Cancer • D-dimer • Diagnostic algorithms • Imaging • Myeloproliferative disorders • Thrombophilias

## Introduction to the Case

Breakthrough (recurrent) popliteal and calf veins DVT developed in a compliant 43-year-old Caucasian female while on rivaroxaban (Xarelto®) 20 mg PO daily. Rivaroxaban was taken within a treatment period for a previously verified bilateral (PE) 5 months earlier. The only medication at the presentation's time was rivaroxaban 20 mg daily in the last 4 months. The fresh VTE was verified by a complete right lower limb Doppler Ultrasound (US). For a detailed description of the clinical presentation of this previously reported case and the analysis refer to [1,2].

## Literature Review

VTE is a complex heterogeneous disease with a significant cause of morbidity and mortality worldwide [1,3]. It is the 3<sup>rd</sup> leading vascular disease [1], a common diagnosis in the Acute and Emergency Rooms (A and E) [4], the 2<sup>nd</sup> most common complication for hospitalized patients, the 2<sup>nd</sup> most common cause of prolonged hospital stay, and the 3<sup>rd</sup> most common cause of in-hospital death [5]. The global burden of VTE is expected to increase because of an aging population, and aging is a risk factor for developing VTE [5]. The health and the economic burdens extend beyond the acute event [6]. DVT is the most common VTE presentation, which commonly occurs in the deep veins of the legs/pelvis [5,6] and can potentially dislodge and causes PE, which is the potentially fatal form of VTE. The clinical presentation of VTE can generally overlap with other clinical diseases, including Post-Thrombotic Syndrome

(PTS) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) [1]. Several diagnostic challenges exist when using the current algorithms for diagnosing DVT/PE, especially for patients belonging to certain subgroups; cancer, pregnancy, recurrent VTE or are on anticoagulation therapy at the time of presentation. Currently, there is no gold standard approach in diagnosing recurrent or breakthrough thrombosis. Accurate diagnostic strategies are needed because of the potential morbidity or mortality risk caused by missing a VTE diagnosis, the risk of bleeding with anticoagulants, and to allow possibly etiology-based treatment by identifying the causes of the new events. This paper represents a review in which several aspects are addressed, and a hypothesis-generated diagnostic algorithm is proposed to reach the diagnosis and may aid in directing management. This algorithm requires validation by future studies and research.

## Recurrent VTE versus Breakthrough VTE

### Recurrent thrombosis

Patients with symptomatic VTE, especially those with unprovoked VTE, have a high risk of VTE recurrence, which continues for many years [5,6]. The definition of recurrent VTE is a hospitalization (admission) or an A and E visit with a primary diagnosis of VTE during the follow-up period. Annual recurrence rates are 5%-10%, with the highest risk being in the first 6-12 months after stopping anticoagulation therapy [7]. VTE recurrence occurs in approximately 5%-7% of patients per year after an initial episode [8]. A meta-analysis [9] of 7515 patients with a first unprovoked VTE event who had completed at least 3 months of anticoagulation treatment found that the long-term risk for recurrent VTE was substantial. The higher risk of recurrence occurs in the 1st year. The VTE recurrence risk reached up to 10.3% in the 1st year after discontinuation of therapy, 25% at 5 years, and 36% at 10 years [9]. This percentage reflects that unprovoked VTE is a chronic disease [9]. Recurrence is also associated with Potential Long-Term Consequences; (PTS) and (CTEPH) [8], which could mimic the symptoms of recurrent VTE [1,10]. Anticoagulation therapy is directed towards VTE's acute event to stop clot propagation, prevent VTE recurrence and other long-term complications [6]. Patients with unprovoked VTE receive

\*Address for Correspondence: Al-Khafaji RA, Department of Oncology, Centre for Cancer and Organ Diseases, Rigshospital, Copenhagen, Denmark, E-mail: rasha.alkhafaji2@gmail.com, ORCID: <https://orcid.org/0000-0003-4577-562X>

**Copyright:** © 2021 Al-Khafaji RA. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Received** 15 February 2021; **Accepted** 09 March 2021; **Published** 16 March 2021

3-6 months of anticoagulation therapy, but traditionally they receive 6 months [9]. Extended anticoagulation therapy reduces the risk of recurrence by at least 80%, but there is still controversy regarding which patient should receive this treatment [5]. This approach is also not undertaken because bleeding may outweigh the benefits of anticoagulation therapy [8]. Patients with a first unprovoked VTE might be expected to derive a small net long-term mortality benefit from continuing anticoagulation over a 10-year horizon. But this must be patient-centered, which considers sex, site of the VTE, the risk of bleeding, and the patient's preference [9]. Interestingly in a meta-analysis [9] of 7515 patients with a 1st unprovoked VTE, if VTE was a DVT, there was a low recurrence rate and thus will not highly benefit from indefinite anticoagulation therapy [9]. Patients with PE had a higher recurrence rate than DVT and may benefit from anticoagulation therapy. Finally, a patient not experiencing VTE recurrence in the first two years of stopping anticoagulant therapy is unlikely to experience a net long-term mortality benefit from restarting thromboprophylaxis [9].

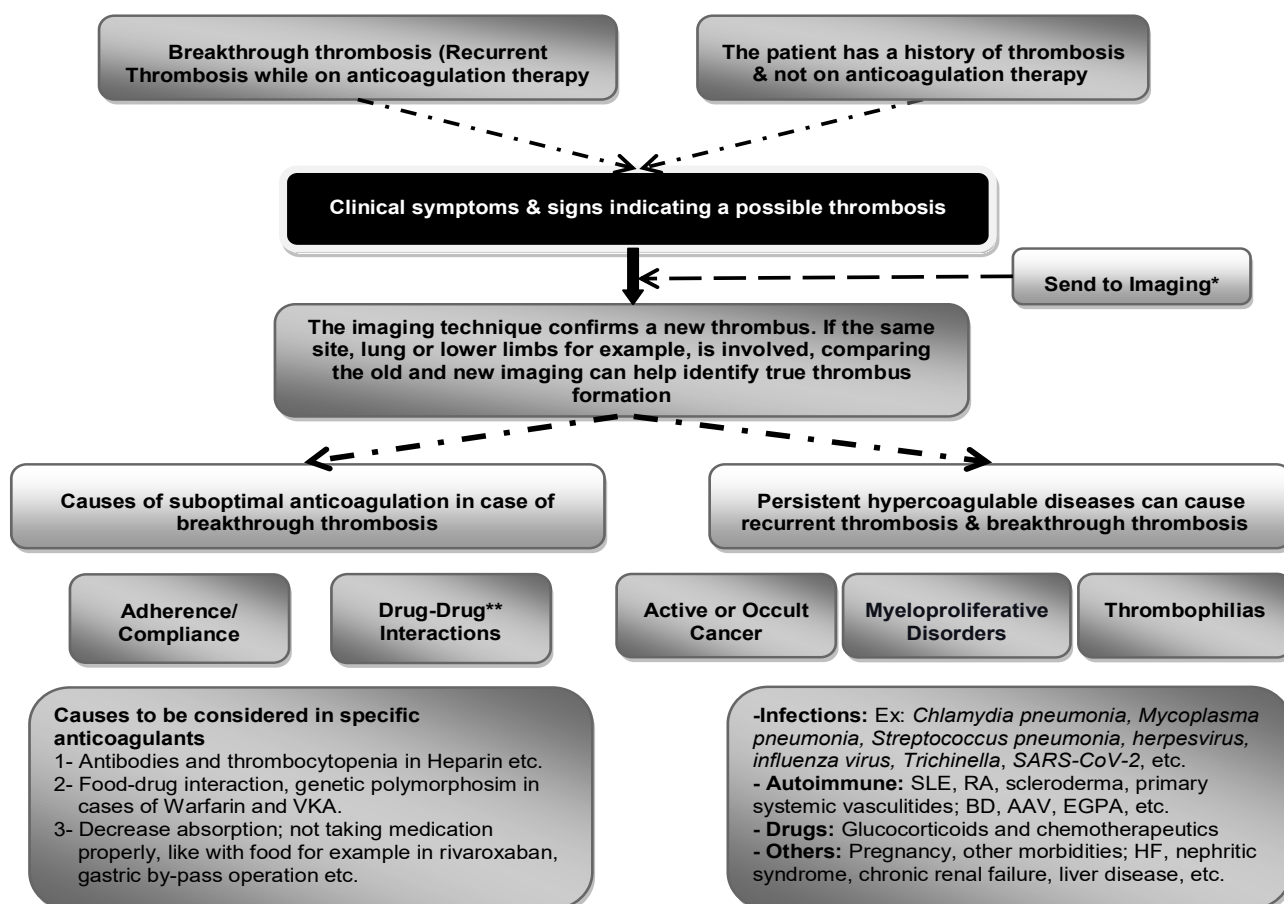
## Breakthrough VTE

Breakthrough thrombosis, or what is known as anticoagulant "failure," refers to the formation of a thrombus while on anticoagulation therapy. VTE involves a prolonged inflammatory process that requires dynamic remodeling and fibrosis. Therefore, several inflammatory cytokines are involved, leading to thrombus' false/true growth in the first period [11]. Detecting incidentally asymptomatic thrombus propagation within the first 30 days of anticoagulation therapy can be seen in up to 30% of patients [11]. This incidental detection should not be regarded as "anticoagulation failure" [11]. Therefore, continuing with the same medication, exclude noncompliance, and a practice of close clinical follow-up and heightened patient vigilance for symptoms of worsening

DVT should be followed [11]. Symptomatic progression is different and should be assessed, and these cases cannot be dismissed. Switching to an alternative anticoagulant and investigating underlying causes should be strongly considered [4,11]. Based on the previous, Olsen et al. suggest the term "breakthrough thrombosis" becomes used specifically for only symptomatic or late (>30 days of starting anticoagulation therapy) thrombus propagation to avoid unnecessary change in anticoagulation therapy. This name changing can help physicians in their approach and avoid an unnecessary change of anticoagulation therapy [11]. Unlike heparin and VKA, early propagation rates with DOACs remain largely unknown [11].

## Causes of recurrent thrombosis and breakthrough thrombosis

Breakthrough thrombosis and recurrent thrombosis could be the cardinal presentation of an underlying disease with thrombogenicity such as active cancer, APLS, vasculitis, etc. [3,10,12] (Figure 1). Breakthrough thrombosis can also result from suboptimal anticoagulation therapy [12] (Figure 1). False therapeutic failures are, in fact, secondary to the patient's non-compliance in terms of doses and mode of intake (with food, after food, food-drug interactions, or simply forgetting to take the pills). On the other hand, true therapeutic failures could be caused either by decreased anticoagulation secondary to drug-drug interactions, genetic dispositions, etc., or by the existence of a hypercoagulable status overcoming the protective effects of the anticoagulation therapy [12] (Figure 1). The hypercoagulable causes seen in Figure 1 are also responsible for recurrence. Malignancy is one of the most common causes of recurrent and breakthrough thrombosis for various reasons [10].



**Notes:** The author generated this hypothetical algorithm based on this review. \*Send to imaging regardless of D-dimer testing. \*\*Physicians cannot remember all the possible drug-drug interactions; therefore, it is possible to use an online drug checker in daily practice to identify interactions and suggestions if internet services are available [2].

**Abbreviations:** AAV: ANCA-Associated Vasculitis, BD: Behçet's Disease, EGPA: Eosinophilic Granulomatosis with Polyangiitis, RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, and VKA: Vitamin K Antagonists.

**Figure 1.** The Hypothesis-Generated Algorithm for diagnosing recurrent VTE or breakthrough VTE while on anticoagulants with their possible etiologies.

## The role of imaging in recurrent and breakthrough thrombosis

The imaging of DVT has evolved from conventional contrast venography and duplex sonography to Computed Tomography (CT)/magnetic resonance venography (MR venography), scintigraphy, and the latest molecular imaging/nanotechnology [13]. An imaging modality, for example, should have the capacity to distinguish acute on chronic DVT from (PTS). The latter develops in 20-50% of patients after DVT [13], and PTS symptoms, such as pain and edema, can mimic a new onset of acute thrombus [13,14]. But it does not require anticoagulant therapy. It is suspected that over 50% of patients with suspected recurrent VTE will have residual venous disease from the initial VTE event, which potentially confounds the diagnosis of a recurrent event [12]. Ultrasound techniques are the mainstay for diagnosing DVT, especially for the lower limbs. (US) is non-invasive with no radiation, is readily available, and cost-effective [14]. Lack of complete compressibility of a venous segment under the probe's gentle pressure is the main ultrasound criterion for diagnosing a first DVT event [14]. But because of the persistence of obstructive post-thrombotic damage, this criterion is difficult to interpret for the diagnosis of a recurrent event [14]. However, an increase of 4 mm or more in vein diameter by two comparative US measurements after vein compression is diagnostic of *in situ* recurrences. In a previously thrombosed vein with residual thrombus, if the increase is between 2-4 mm, it is unclear, requiring repetition after 1 week. In comparison, an increase of 2 mm or less enables recurrence to be ruled out [14]. Several technical difficulties are to be considered regarding the previous, such as distal DVT because the veins are < 5 mm, ilial level, and pharmacomechanical recanalization, where the thickening is related to the wall rather than the thrombus. Non-compressibility of a previously compressible venous segment is a strong and well-established criterion for the diagnosis of recurrent DVT [14]. The criteria using thrombus' echogenicity, increased length of the thrombus, and Doppler venous flow signal are non-validated criteria [14,15]. It is necessary to point out that the US can give false-positive results in compression by pelvic masses or false negative in calf DVT. Also, it is operator dependant, and expertise is required [13,15]. Imaging alone without the use of preclinical probability and D-dimer is appropriate in hospitalized patients [15].

Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a more promising alternative when applied as a first- or second-line imaging test than the US for detecting recurrent/breakthrough thrombosis because it can detect acute ipsilateral recurrent DVT and distinguish it from at least 6-month-old chronic residual thrombi in the leg veins when recurrence is not suspected clinically [13,14]. Also, it has its advantages in that it can examine both legs in less than 5 minutes, not operator dependant and have a high interobserver agreement and no radiation [13]. However, it is limited in that it can miss an acute thrombus in the very early phases, where compression UL scanning has the advantage of detecting it [13]. Also, MRI is less favorable than CT scanning for evaluating acute VTE because of its cost, lack of availability, and technical limitation in assessing the calf veins [13]. Other modalities have also been explored; for example, Technetium Tc-99m-apcitide scintigraphy can potentially differentiate old from acute thrombus, but the technique is limited because it also depends on the training and experience of the interpreters [13]. 18F-FDG PET/CT could be used to assess the thrombus's age because the metabolic activity in thrombosed vein segments decreases with DVT's time onset [13]. Specific imaging techniques addressing recurrent/breakthrough in the lung and other sites are not covered in this review.

## The role of D-dimer testing

A high-quality D-dimer can be used along with Pretest Probability Scoring (PTP), based on Wells' score, to direct management of a possible VTE in outpatients [1,14-16]. D-dimer testing's value resides in a negative result and should only be used when there is a clinical suspicion of VTE; otherwise, a positive test result could divert the clinician from finding the patient's actual diagnosis [15]. In low and moderate PTP, a negative high-quality D-dimer testing can rule out VTE, while a positive result requires imaging [1]. But D-dimer testing has numerous clinically relevant limitations [1]. Aging, cigarette smoking, or other diseases such as cancer, infection, and rheumatic diseases can physiologically elevate D-dimer [1,16]. Also, standardization is

not possible with D-dimer because of various methodologies used in D-dimer testing. Results are also affected by the presence of interfering substances such as bilirubin and triglycerides. The sensitivity of D-dimer also depends on the site and size of the thrombus [1]. A study carried by Grégoire Le Gal, et al. [16] showed that D-dimer testing might have limited clinical usefulness in detecting the recurrence of VTE and suspected PE because it remains elevated after the completion of 6-month anticoagulation therapy for the first episode of VTE [16]. This property has been utilized to consider extending the anticoagulation therapy beyond the 6 months if the D-dimer testing is positive after anticoagulation withdrawal [17]. A study carried by Cristina Legnani, et al. [17] showed that the rate of positive D-dimer assessed during anticoagulation was significantly higher in patients treated with Direct Oral Anticoagulant (DOAC)s than with warfarin. Whether Vitamin K Antagonists (VKA) and (DOAC) have different effects on D-dimer assay, the data is currently scarce to answer this [1]. It is relevant to point out that the patient referenced in this review [1,2] had low-risk PTP and the high-quality D-dimer testing was negative twice, measured 2 days apart. It was the complete US that confirmed the breakthrough DVT.

## Causes of Recurrent and Breakthrough Thrombosis

### Sub-therapeutic causes that could lead to breakthrough thrombosis

Despite anticoagulation therapy, an occurrence of a new thrombus is possible [4,10,11,18,19] (Figure 1). Physicians should be aware that 2% of patients compliant with therapeutic anticoagulation experience recurrent venous thromboembolism [4,10,11]. Patients in large DOAC clinical trials, despite adequately anticoagulated, had a 2% occurrence of thromboembolism [19].

**Heparin:** Heparin produces its major anticoagulation effects by inactivating thrombin and factor X through an Antithrombin (AT)-dependent mechanism [20]. Resistance to heparin should be considered when there is a need for more than 35000 units in 24 hours to achieve a target Partial Thromboplastin Time (PTT) or if the dose is 25 units/kg/hr. This resistance could be due to an anti-thrombin deficiency, the elevation of factor VIII and/or fibrinogen, the elevation of Heparin-binding proteins, or increased heparin clearance [20]. In such clinical cases, Argatroban is a good alternate agent for systemic +anticoagulation [20]. Heparin-Induced Thrombocytopenia (HIT) is an IgG antibody-mediated adverse reaction that leads paradoxically to *in vivo* activation of platelets and the coagulation system [21]. This activation could lead to DVT and PE, which lower-limb DVT is HIT's most common complication [21]. Inappropriate treatment of HIT-associated DVT with warfarin leads to microvascular thrombosis and tissue necrosis because of the impaired ability of the protein C natural anticoagulant pathway to down-regulate thrombin generation. Warfarin in these cases can cause the DVT to progress to limb gangrene [21]. Even in the absence of HIT, PE itself can be complicated by thrombocytopenia, thus posing a diagnostic challenge. This set of patients requires an alternative treatment until antibody testing is obtained [21]. Unfractionated heparin is more likely to cause HIT antibody formation, as well as clinical HIT, than does Low-Molecular-Weight Heparin (LMWH) [21]. Thrombocytopenia usually begins 5-10 days after starting heparin, but an acute decrease of the platelet count can begin in patients who have recently taken heparin in the past 100 days [21]. Danaparoid and Lepirudin can be used to treat thrombosis associated with HIT and performing a lower US to exclude a subclinical thrombosis is warranted [20]. Details on how to treat clinical cases with HIT are not covered in this review.

**Vitamin K Anticoagulants (VKA) and Direct Oral Anticoagulant (DOAC):** VKAs interfere with the  $\gamma$ -carboxylation of glutamate residues in Factors II, VII, IX, and X [2,22-24]. VKAs have unpredictable pharmacokinetics and pharmacodynamics [2,22,24-26], interact with drugs and food, and are affected by genetic polymorphism [2]. Therefore, they have a narrow therapeutic window and exhibit intra-individual variation. Treating patients with VKA requires constant monitoring through International Normalized



Ratio (INR). INR requires 4-6 weeks until it is stable at 2-3. Therefore, 1 or several sub-therapeutic INR readings in this period are common [10]. Beyond this period, a sub-therapeutic INR in a compliant patient must be checked. On the other hand, the (DOAC) group has predictable and dose-dependent pharmacokinetics as one of their key strengths [22]. They could be given in fixed doses with adaptation according to renal function, and according to the specific cause they are being used for [2]. The potential for sub-therapeutic or supra-therapeutic drug activity to go undetected is more common with the DOACs because neither testing for drug levels nor efficacy measures are widely available, nor are these tests usually performed if present. Patients in large DOAC clinical trials, despite adequately anticoagulated, had 2% thromboembolism occurrence [19]. In a rivaroxaban review [2], the author concluded that although rivaroxaban has fewer drug-drug interactions than VKA, rivaroxaban-drug interactions exist, which might alter rivaroxaban's efficiency [2]. Also, research exploring the effects of genes playing a role in rivaroxaban's distribution, metabolism, and excretion, such as ABCG1, ABCG2, CYP3A4, CYP3A5, is still scarce [2].

### Underlying pathologies with hypercoagulability

More than one cause leading to a state of hypercoagulability can coexist, resulting in that the overall risk of developing thrombosis can exceed the sum of the separate effects. A thorough medical history may help elucidate the presence of such multiple risk factors (Figure 1). Not all the thrombogenic pathologies involved are covered. Still, the author attempts to cover common pathologies physicians could encounter in daily practice and consider investigating their presence because the fresh VTE could signal an underlying undiagnosed pathology.

**Cancer and cancer therapy:** They are intimately related to thrombosis [27]. Thrombosis is a leading cause of mortality in cancer patients irrespective of stage [27,28]. Arterial, venous, and Disseminated Intravascular Coagulation (DIC) thrombosis have been reported with cancer/cancer therapy, but VTE is more common [27]. VTE could be the first clinical presentation of cancer. A review done by Chih-Hao Chao, et al. [29] showed that 3.7-10% of patients with unprovoked VTE would be diagnosed with occult cancer within 1 year. The same review showed that the incidence of diagnosing occult cancer is directly correlated with increased age [29]. In a nationwide observational study in Denmark from January 2000 through December 2015, it was shown that the highest rate of VTE recurrence was seen in cancer patients [30]. At a 10-year follow-up, the recurrence risk was similar for patients with unprovoked VTE and cancer-related VTE [30]. Multiple and overlapping mechanisms interact and explain the increased incidence of Cancer-Associated Thrombosis (CAT). Cancer cells produce Tissue Factors (TF) that activate and form complexes with factor VII, which leads to activating factor X. The latter could also be activated directly by procoagulants produced by cancer cells. The amplified cascade of coagulation activates platelets, which leads to CAT. Therefore, cancer is a state of hypercoagulation due to coagulopathy, hypoxia, inflammation, and the production of various bioactive products such as adhesion factors, Plasminogen Activator Inhibitor (PAI)-1, etc. [27]. These mechanisms are employed by cancer to survive, which can also lead to its growth, metastases and could also be responsible for thrombosis formation [27].

Several factors involved in cancer/cancer therapy could play a role in the high incidence of thrombosis. These factors could be cancer-related, such as the presence of metastasis, cancer type; brain, lung, gastric, pancreas, renal, and ovarian have high thrombosis incidence, while histologically adenocarcinoma carries an increased risk of VTE [27]. Platinum preparations, multi-targeted tyrosine kinase inhibitors, taxane-based anticancer agents, immunomodulators, and angiogenesis inhibitors increase thrombosis risk [27]. Patient and treatment-related factors also could contribute to thrombosis, such as African ethnicity, malnutrition, dehydration, bedridden, surgery, vascular injury caused by chemotherapy, radiotherapy, catheters, coexisting comorbidities of the lung, heart, and kidney, etc. [27]. Therefore, Failure of anticoagulation in treating CAT is common [28]. For patients who experience breakthrough thrombosis despite compliance to anticoagulants and are not diagnosed with a hypercoagulable disease, investigating for an undiagnosed cancer is warranted. Clinicians should always have a low threshold for occult cancer despite not necessarily improving survival. A history and a physical

examination can help decide to investigate for occult cancer [12]. Treatment of thrombosis is challenging in a cancer patient because cancer has both intrinsic thrombotic activity and bleeding tendency [3]. Bleeding is a frequent complication because of thrombocytopenia caused by chemotherapy or the underlying malignancy, liver metastases, or procoagulation leading to DIC [28]. Therefore, treating thrombosis in any cancer patient requires an individualized assessment to consider the risk of bleeding against the severity of the thrombotic event and risk for recurrent VTE [28].

**Myeloproliferative disorders, thrombophilias, and genetic predispositions:** Thrombophilia is a term that includes any inherited and acquired disorders associated with an increased tendency to VTE [31]. The JAK2 V617F mutation is an acquired somatic mutation, low in the general population [32]. This mutation increases the risk of any cancer, including hematological cancer [32]. It is present in most patients with myeloproliferative neoplasms (MPN). JAK2 V617F mutation is present nearly in 100% of the patients with polycythemia vera and about 50% of patients with essential thrombocythosis and primary myelofibrosis [32]. Thromboses in atypical sites as intra-abdominal or intracranial veins could be the cardinal signs of myeloproliferative diseases. Therefore, molecular profiling with analysis of JAK2, Calreticulin (CALR), and Myeloproliferative Leukemia (MPL) mutations can be of value [10]. A study by Mihaela Tevet, et al. [31], involving 192 patients with myeloproliferative disorders, showed that the thrombotic risk was higher in the JAK2 V617F-mutated subgroup of the cohort, and the presence of inherited thrombophilia further increased thrombosis; especially by the presence of lupus anticoagulant and mutated FV Leiden. The effect of this mutation in diagnosing MPN in patients with unprovoked recurrent VTE has been explored in a study carried by Iannotti J, et al. [33]; it was illustrated that in the cohort of 372 with unprovoked recurrent VTE, 21% of the patient, who their recurrence was while on anticoagulation therapy (breakthrough thrombosis), had JAK2V617F mutation [33]. Patients presenting with an abnormal Complete Blood Count (CBC) at the time of breakthrough thrombosis should receive a follow-up CBC. If thrombocytosis, leukocytosis, and/or polycythemia are persistent, screening for JAK2 V617F and (CALR) mutations is warranted [33]. Genes involved in hemostasis could be involved in thrombophilia and subsequent VTE, strokes, and myocardial infarctions [34]. The clinical manifestations of hereditary genetic mutations causing thrombophilia may vary between individuals [35] because genetic alterations have been shown to interact with other risk factors. A genetic variant that has been correlated to increase risk of thrombosis is a single-nucleotide G4A transition, at position 20210 (c.20210G4A) in the prothrombin gene because it is associated with increased prothrombin levels [34]. The c.1691G4A is the most common single point mutation involving the Factor V Leiden studied. This mutation results in a resistance to activated protein C [34]. The polymorphism, c.143G4T, in the gene coding for factor XIII seems to result in its inactivation, which could contribute to thrombotic disorders [34]. Protein C/S deficiency usually leads to DVT, including lower limb DVT, while arterial thrombosis is relatively rare [35].

**Infection:** This is an independent risk for developing thromboembolic diseases, such as DVT, PE, MI, and stroke [36]. Various pathogens have been involved in thromboembolic events such as *Staphylococcus aureus*, *Neisseria meningitidis*, *Escherichia coli*, *Haemophilus influenza*, *Epstein-Bar virus*, *cytomegalovirus*, *ebola*, *varicella*, *hepatitis*, *HIV*, *SARS-CoV-2*, *Ascaris lumbricoides*, *Toxocara*, *Schistosoma mansoni*, etc. [36-38]. Infection raises the risk of thrombosis by 2-20 times, which both host and pathogen-derived factors influence the ultimate risk of developing thrombosis [36]. Many pathogens target hemostasis and coagulation by various mechanisms, with more severe infections promoting greater inflammation and higher risks of thrombotic complications [36,37]. Sometimes thrombi could be detected in one site weeks after infection [36]. Sepsis often occurs without an infective agent being identified, yet there is an excessive Systemic Inflammatory Response Syndrome (SIRS) and is frequently associated with (DIC). Treatment of thrombosis in case of infection should be tailored with a patient-centered approach based on individual risk assessment. Until now, there is no consensus on a systematic approach for treating thrombosis in infections. For example, for those affected by COVID-19, a thrombotic disease is reported as high as 31%, but there are different approaches among countries when initiating anticoagulation therapy [37].

**Table 1.** Essential points regarding autoimmune diseases and thrombosis.

S. No.	The Variable	Comments
1	Thrombosis	These diseases are not infrequently associated with arterial or venous thromboembolic events [39]. An association between systemic autoimmune diseases and (DVT)/VTE has been established [40].
2	The Pattern of Thrombosis	Thrombosis targeting the venous bed and/or arterial bed differs from one autoimmune disease to another [39]. The ultimate thrombotic risk depends on the presence of other factors like DM, smoking, undiagnosed thrombophilias, and other comorbidities [39]. Thromboses in atypical sites as intra-abdominal or intracranial veins could also be found in these diseases.
3	Etiopathogenesis of Thrombosis	The etiopathogenesis of increased risk of thrombosis involves multiple contributors, and the pathogenesis is still not entirely clear [40]. But chronic inflammation and immune system impairment are considered the main pathogenetic mechanisms [39].
4	Immunosuppressive Therapies	Some case reports and observational studies have reported vascular complications associated with immunosuppressive therapies. Thrombosis because of glucocorticoids has been backed with evidence. Other drugs, monoclonal antibodies, endovenous immunoglobulins, and even High-dose IVIg, may also be related to thrombosis [39].
5	Vitamin K Antagonists (VKA)	When used in Antiphospholipid Syndrome (APS) patients, VKAs are used for VTE treatment and secondary thromboprophylaxis with a target INR: 2.0–3.0. But even with this strategy, there is only an 80-90% risk reduction of recurrent VTE [41].
6	The International Normalized Ratio (INR)	A minority of patients with APS produce antibodies against tissue factors resulting in false INR. Also, sometimes INR could be non-reliable because point-of-care instruments are variable [10].
7	Direct Oral Anticoagulants (DOAC)	In APS: The European Medicines Agency (EMA) recommends against the use of DOACs, especially in patients with triple positivity for aPL [41,42]. The latter subgroup and those with previous arterial manifestations are more prone to recurrent thrombosis when treated with DOACs [41].

**Table 2.** Other scenarios to consider as a cause of recurrent and breakthrough thrombosis.

S. No.	Clinical Scenario	Comments
1	Vascular Malformations	In almost all vascular malformations, coagulopathic abnormalities can occur but are most significant in diffuse and multifocal Venous Malformations (VMs), Lymphatic Venous Malformation [LVM], and Capillary Lymphatic Venous Malformation [CLVM]) [43]. These malformations have Localized Intravascular Coagulopathy (LIC), which can sometimes progress to (DIC) [43]. The most prevalent Vascular Anomalies (VMs). These anomalies are low flow [44]. Asymptomatic thrombosis, superficial thrombosis, and DVT are common findings in pure VMs [43,44].
2	Pregnancy	It is a normal physiological process, but there is a 4-5-fold increase in developing VTE [45], which can occur at any trimester [45]. Pelvic thrombosis is more common, as well as left side DVT [45]. There is a higher risk of developing VTE in postpartum, and (PE) was the leading cause of maternal mortality in the USA and UK [45].
3	Common Comorbidities	Heart Failure (HF) patients have combined thromboembolic risks, which VTE is one aspect [46,47] with the risk being especially high after a new HF diagnosis [47], nephrotic syndrome [48,49], and Chronic renal failure [50].
4	Thrombophilias	Not all causes of thrombophilia are covered in this review. For more details in this regard, refer to [51].

### Autoimmune disorders and others:

- In regards to autoimmune diseases and thrombosis (Table 1) [39-42].
- **Others:** (Table 2) [43-51]

## Back to Our Patient

On a consented follow-up [1]: tests for thrombophilia and (APS) were negative. Cancer was not investigated because of a lack of clinical suspicion. Whether rivaroxaban's pharmacokinetics and pharmacogenetics had created a state of decreased anticoagulation was a question that remained unanswered [2]. This case emphasizes the complexity of VTE and that there could be different risk profiles within each patient due to potentially considerable heterogeneity within alterations to the coagulation system.

## Discussion and Conclusion

The current diagnostic algorithms for (DVT) and (PE) by the American Society of Hematology (ASH) and the National Institute for Health and Care Excellence (NICE) have shown limitations in patients who are on anticoagulants or having recurrent VTE. These algorithms use Wells' Criteria for DVT and PE to calculate the Pretest Probability (PTP), which stratifies the patient's risk of having DVT/PE into 3 categories; low, moderate, and high. Unlike Wells' Criteria for PE, which in its scoring considers \*Previous, objectively diagnosed PE or DVT\*, Wells' Criteria for DVT includes only \* a previously documented DVT\*. Scenarios of isolated PE without DVT have been reported. Also, neither Wells' Criteria for DVT nor PE consider other forms of previously objectified VTE, which potentially could affect the scoring. It is very common for patients with prior VTE to present with suspected recurrence. Although breakthrough VTE while on anticoagulants is not common, 2% of compliant patients experience it. Both breakthrough and recurrent VTE could herald the

presentation of an underlying thrombogenicity as cancer, myeloproliferative disorders, autoimmune disease, thrombophilia, etc. Therefore, physicians should have a low threshold for initiating the evaluation of suggestive clinical presentations to exclude the presence of possibly recurrent and breakthrough thrombosis. This evaluation may also help in elucidating the underlying pathology/pathologies involved in this fresh thromboembolic event. It is only through accurate diagnosis can treatment become more patient-centered and etiology-based. There is no gold standard approach in diagnosing the occurrence of new thrombotic events in the face of therapeutic anticoagulation. Missing the diagnosis of VTE carries potentially a death risk, while the use of anti-coagulants carries a risk of bleeding. Therefore, accurate diagnostic strategies are needed. Based on this review, the author concludes that imaging to diagnose or exclude recurrent VTE conclusively is to be used regardless of D-dimer testing. Also, because most cases of diagnosing recurrent DVT are residuals from prior VTE, a baseline imaging on discontinuation of anticoagulation treatment is recommended. Finally, the author constructs a flowchart targeted to diagnose patients who exhibit clinical features due to recurrent VTE or breakthrough VTE while on anticoagulants. The suggested algorithm also illustrates possible causes for recurrent and breakthrough VTE. Whether these suggestions and the hypothesis-generated algorithm effectively decrease the incidence of missed diagnosis and subsequently improve clinical outcomes and practice, only specifically designed studies can answer and validate these. Further studies can also allow gradual accumulation of relevant data, and the author hopes the review and the hypothesis-generated algorithm can contribute to this.

## References

1. Rasha A. Al-Khafaji and Louise Schierbeck. "Deep Venous Thrombosis in a Patient with a Moderate Pretest Probability and a Negative D-Dimer Test: A Review of the Diagnostic Algorithms." *J Blood Med* 11 (2020): 173-184.

2. Al-Khafaji, Rasha. "Developing Deep Venous Thrombosis while on Rivaroxaban: A Review of Rivaroxaban." *Clin Case Rep* 10 (2020): 7.
3. Van Es, J., Cheung, Y., van Es, N., Klok, F., Dronkers, C., and ten Wolde, M. et al. "Short-Term Prognosis of Breakthrough Venous Thromboembolism in Anticoagulated Patients." *Thromb Res* 187 (2020): 125-130.
4. Leah Hatfield, B., Harry W. Severance, M., Mark L. Plaster, J., and Michael Lynch, M. (2017). Recurrent VTE Despite Anticoagulation | Emergency Physicians Monthly. Retrieved 7 July 2020, from <https://epmonthly.com/article/recurrent-vte-despite-anticoagulation/>
5. Jeffrey Weitz and Alok Khorana. "Treatment Challenges in Venous Thromboembolism: An Appraisal of Rivaroxaban Studies." *Thromb Haemost* 118 (2018): 23-33.
6. Celeste B. Burness and Caroline M. Perry. "Rivaroxaban: A Review of Its Use in the Treatment of Deep Vein Thrombosis or Pulmonary Embolism and the Prevention of Recurrent Venous Thromboembolism." *Drugs* 74 (2014): 243-262.
7. Alex C. Spyropoulos, Veronica Ashton, Yen-Wen Chen and Bingcao Wu, et al. "Rivaroxaban versus Warfarin Treatment Among Morbidly Obese Patients with Venous Thromboembolism: Comparative Effectiveness, Safety, and Costs." *Thromb Res* 182 (2019): 159-166.
8. Philip S. Wells, Martin H. Prins, Jan Beyer-Westendorf and Anthonie W.A. Lensing, et al. "Health-Care Cost Impact of Continued Anticoagulation with Rivaroxaban vs Aspirin for Prevention of Recurrent Symptomatic VTE in the EINSTEIN-CHOICE Trial Population." *Chest* 154 (2018): 1371-1378.
9. Faizan Khan, Alvi Rahman, Marc Carrier and Clive Kearon, et al. "Long Term Risk of Symptomatic Recurrent Venous Thromboembolism after Discontinuation of Anticoagulant Treatment for First Unprovoked Venous Thromboembolism Event: Systematic Review and Meta-Analysis." *BMJ* 12 (2019): 4363.
10. Schulman, Sam. "How I Treat Recurrent Venous Thromboembolism in Patients Receiving Anticoagulant Therapy." *Blood* 129 (2017): 3285-3293.
11. Sven R. Olson, Joseph J. Shatzel and Thomas G. DeLoughery. "Asymptomatic "Breakthrough" Thrombosis and Anticoagulant "Failure": Keep Calm and Carry On." *Res Pract Thromb Haemost* 3 (2019): 498-502.
12. Marc A. Rodger, Sebastien Miranda, Aurelien Delluc and Marc Carrier. "Management of Suspected and Confirmed Recurrent Venous Thrombosis While on Anticoagulant Therapy: What next?." *Thromb Res* 180 (2019): 105-109.
13. Gita Yashwantrao Karande, Sandeep S. Hedgire, Yadiel Sanchez and Vinit Baliyan, et al. "Advanced Imaging in Acute and Chronic Deep Vein Thrombosis." *Cardiovasc Diagn Ther* 6 (2016): 493-507.
14. Mario Maufus, Antoine Elias, Marie-Thérèse Barrellier and Gilles Pernod. "Diagnosis of Deep Vein Thrombosis Recurrence: Ultrasound Criteria." *Thromb Res* 161 (2018): 78-83.
15. Philip S. Wells, Ryma Ihaddadene, Aoife Reilly and Melissa Anne Forgie. "Diagnosis of Venous Thromboembolism: 20 Years of Progress." *Ann Int Med* 168 (2018): 131.
16. Grégoire Le Gal, Marc Righini, Pierre-Marie Roy and Oliver Sanchez, et al. "Value of D-Dimer Testing for the Exclusion of Pulmonary Embolism in Patients with Previous Venous Thromboembolism." *Arch Int Med* 166 (2006): 176.
17. Cristina Legnani, Ida Martinelli, Gualtiero Palareti and Alessandro Ciavarella, et al. "D-Dimer Levels during and after Anticoagulation Withdrawal in Patients with Venous Thromboembolism Treated with Non-Vitamin K Anticoagulants." *Plos One* 14 (2019): 219751.
18. Thomas L. Ortel, Ignacio Neumann, Walter Ageno and Rebecca Beyth, et al. "American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism." *Blood Adv* 4 (2020): 4693-4738.
19. Graham McIlroy, Neil Smith, Anand Lokare and Karen Beale, et al. "Treatment Failure in Patients Receiving Direct Oral Anticoagulants: Clinical Management and Outcomes from a Single-Centre Review of 59 Consecutive Patients." *Blood* 132 (2018): 5058-5058.
20. Adam B. King, Anne E. O'Duffy and Avinash B. Kumar. "Heparin Resistance and Anticoagulation Failure in a Challenging Case of Cerebral Venous Sinus Thrombosis." *Neurohospital* 6 (2016): 118-121.
21. Warkentin, Theodore. "Venous Thromboembolism in Heparin-Induced Thrombocytopenia." *Curr Opin Pulmon Med* 6 (2000): 343-351.
22. Elisabeth Perzborn, Susanne Roehrig, Alexander Straub and Dagmar Kubitz, et al. "The Discovery and Development of Rivaroxaban, An Oral, Direct Factor Xa Inhibitor." *Nat Rev Drug Disc* 10 (2010): 61-75.
23. Meyer Samama, Geneviève Contant, Theodore E Spiro and Elisabeth Perzborn, et al. "Laboratory Assessment of Rivaroxaban: A Review." *Thromb J* 11 (2013): 11.
24. Zi-Kai Song, Hongyan Cao, Haidi Wu and Qi Wei, et al. "Current Status of Rivaroxaban in Elderly Patients with Pulmonary Embolism (Review)." *Exp Therap Med* 26 (2020): 01.
25. Nishank Jain and Robert F. Reilly. "Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease." *Clin J Am Soc Nephrol* 14 (2018): 278-287.
26. Stavros K. Kakkos, George I. Kirkilesis and Ioannis A. Tsolakis. "Editor's Choice-Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials." *Euro J Vasc Endovasc Surg* 48 (2019): 565-575.
27. Mikio Mukai and Toru Oka. "Mechanism and Management of Cancer-Associated Thrombosis." *J Cardiol* 72 (2018): 89-93.
28. Agnes Y. Y. Lee and Erica A. Peterson. "Treatment of Cancer-Associated Thrombosis." *Blood* 122 (2013): 2310-2317.
29. Chih-Hao Chao, Hsin-Yi Wang and Chia-Hung Kao. "Occult Cancer and Thromboembolism: Current Epidemiology and its Practical Implication." *Polish Arch Int Med* 27 (2018): 04.
30. Ida Ehlers Albertsen, Peter Brønnum Nielsen, Mette Søgaard and Samuel Zachary Goldhaber, et al. "Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study." *Am J Med* 131 (2018): 1067-1074.
31. Mihaela Tevet, Razvan Ionescu, Cornel Dragan and Anca Roxana Lupu. "Influence of the JAK2 V617F Mutation and Inherited Thrombophilia on the Thrombotic Risk among Patients with Myeloproliferative Disorders." *Med* 10 (2015): 27-32.
32. Camilla Nielsen, Henrik S. Birgens, Børge G. Nordestgaard and Stig E. Bojesen. "The JAK2 V617F Somatic Mutation, Mortality and Cancer Risk in the General Population." *Haematol* 96 (2010): 450-453.
33. Jean-Christophe Iannotto, Aurélie Chauveau, Dominique Mottier and Valérie Ugo, et al. "JAK2V617F and Calreticulin Mutations in Recurrent Venous Thromboembolism: Results from the EDITH Prospective Cohort." *Ann Hematol* 96 (2016): 383-386.
34. Eva Terni, Nicola Giannini, Marco Brondi and Vincenzo Montano, et al. "Genetics of Ischaemic Stroke in Young Adults." *BBA Clin* 3 (2015): 96-106.
35. Pingping Li and Chao Qin. "Recurrent Cerebellar Infarction Associated with Hereditary Heterozygous Protein C Deficiency in a 35-year-old Woman: A Case Report and Genetic Study on the Pedigree." *Exp Therap Med* 25 (2018): 01.
36. Nonantzin Beristain-Covarrubias, Marisol Perez-Toledo, Mark R.

- Thomas and Ian R. Henderson, et al. "Understanding Infection-Induced Thrombosis: Lessons Learned from Animal Models." *Front Immunol* 10 (2019): 5.
37. Juan Simon Rico-Mesa, Daniel Rosas, Ashkan Ahmadian-Tehrani and Averil White, et al. "The Role of Anticoagulation in COVID-19-Induced Hypercoagulability." *Curr Cardiol Rep* 22 (2020): 7.
  38. Paul R. J. Ames, Giuseppina Aloj and Fabrizio Gentile. "Eosinophilia and Thrombosis in Parasitic Diseases: An Overview." *Clin App Thromb* 17 (2011): 33-38.
  39. Antonella Scalera, Giacomo Emmi, Danilo Squatrito and Lucia Ciucciarelli, et al. "Thrombosis in Autoimmune Diseases: A Role for Immunosuppressive Treatments?." *Sem Thromb Hemost* 42 (2016): 650-661.
  40. Hiromichi Tamaki and Atul Khasnis. "Venous Thromboembolism in Systemic Autoimmune Diseases: A Narrative Review with Emphasis on Primary Systemic Vasculitides." *Vasc Med* 20 (2015): 369-376.
  41. Amine Ghembaza and David Saadoun. "Management of Antiphospholipid Syndrome." *Biomed* 8 (2020): 508.
  42. Hannah Cohen, Maria Efthymiou and David A. Isenberg. "Use of Direct Oral Anticoagulants in Antiphospholipid Syndrome." *J Thromb Haemost* 16 (2018): 1028-1039.
  43. Adams, Denise. "Special Considerations in Vascular Anomalies: Hematologic Management." *Clin Plast Surg* 38 (2011): 153-160.
  44. van Es, J., Kappelhof, N., Douma, R., Meijers, J., Gerdes, V., and van der Horst, C. "Venous Thrombosis and Coagulation Parameters in Patients with Pure Venous Malformations." *Neth J Med* 75 (2017): 328-334.
  45. Springel, E. Thromboembolism in Pregnancy: Practice Essentials, Background, Pathophysiology. (2018) Retrieved 21 February 2021, from <https://emedicine.medscape.com/article/2056380-overview>
  46. Larsen, Torben. "Risk of Venous Thromboembolism in Patients with Heart Failure." *Lancet Haematol* 3 (2016): 6-7.
  47. Nathaniel R. Smilowitz, Qi Zhao, Li Wang and Sulena Shrestha, et al. "Risk of Venous Thromboembolism after New Onset Heart Failure." *Scient Rep* 9 (2019): 01.
  48. Raymond Lin, Georgina McDonald, Todd Jolly and Aidan Batten, et al. "A Systematic Review of Prophylactic Anticoagulation in Nephrotic Syndrome." *Kidney Int Rep* 5 (2020): 435-447.
  49. Aparna Basu, Shriyanka Jain, Dhruvan Patel and Geeta Bodapati, et al. "Failure of Anticoagulation in a Case of Nephrotic Syndrome with Recurrent Thromboembolism." *Chest* 148 (2015): 983.
  50. Hsueh-Yi Lu and Kuang-Ming Liao. "Increased Risk of Deep Vein Thrombosis in End-Stage Renal Disease Patients." *BMC Nephrol* 19 (2018): 01.
  51. Gian Luca Salvagno, Chiara Pavan and Giuseppe Lippi. "Rare Thrombophilic Conditions." *Ann Trans Med* 6 (2018): 342-342.

**How to cite this article:** Rasha A. Al-Khafaji. "Recurrent Venous Thrombosis and Breakthrough Thrombosis: A Narrative Review." *Clin Case Rep* 11 (2021): 1428.