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Challenges in the Laboratory Diagnosis of Thrombophilia: An In-Depth Review of Current Issues and Approaches

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Abstract

Venous thromboembolic disease (VTD) is influenced by various biological, medical, and ecological risk factors, with thrombophilia representing an acquired or hereditary predisposition to venous thromboembolism (VTE). The complexity of identifying suitable candidates for thrombophilia testing and interpreting results greatly complicates clinical management.This review evaluates traditional inherited thrombophilia, including deficiencies in natural anticoagulants and mutations such as factor V Leiden and prothrombin G20210A. It emphasizes the necessity of molecular diagnostics over traditional plasma tests, particularly in patients undergoing direct oral anticoagulant (DOAC) therapy. The review also discusses the timing of thrombophilia testing and the role of genotyping.The findings reveal that the presence of DOACs can significantly interfere with laboratory assays for thrombophilia. Functional assays for antithrombin, protein C, and protein S demonstrate variability in sensitivity to DOACs, leading to potential false-negative results. The review highlights the importance of neutralizing DOACs before testing to ensure accurate results and explores emerging adsorbent methods to eliminate DOAC interference.The laboratory diagnosis of hereditary thrombophilia is increasingly challenging due to the widespread use of DOACs. Enhanced understanding of how these medications affect testing is crucial for accurate diagnosis and treatment. The review suggests that specialized laboratories should conduct thrombophilia assessments in patients on DOACs to improve diagnostic accuracy and clinical outcomes.

Keywords: *Thrombophilia, Venous Thromboembolism, Direct Oral Anticoagulants, Laboratory Diagnosis, Genetic Testing.*

Introduction

Biological, medical, and ecological risk factors lead to venous thromboembolic disease (VTD), a complex illness. Biological thrombophilia refers to the existence of an acquired or hereditary biological risk factor that predisposes the patient to venous thromboembolism (VTE) [1]. Jean Connors said in a prior study on this subject [2]: "While conducting thrombophilia tests is straightforward, identifying the appropriate candidates for testing and interpreting the results is complex." An evaluation of thrombophilia may be beneficial for the propositus and assist in determining the benefit/risk ratio for the length of anticoagulant therapy. In certain instances, including antithrombin (AT) shortages, it may be beneficial for symptomatic patients undergoing heparin treatment (escalating heparin dosages to attain beneficial anticoagulation) as well as asymptomatic family members, particularly women of reproductive age (to prevent thrombosis during gestation and while using estrogen contraceptives).

Traditional inherited thrombophilia encompasses loss-of-function variants in the genes encoding natural anticoagulant proteins, antithrombin (AT), protein C (PC), and protein S (PS), as well as gain-of-function mutations in the genes for factor V (factor V Leiden (FVL)) and prothrombin (FII) (F2 c.*97G>A; formerly G20210A) [1]. Uncommon fetal thrombophilias are documented in the literature, including genetically induced elevated cholesterol levels, coagulation factors VIII and IX, and hypodysfibrinogenemia [2-4]. Individuals with hereditary hypodysfibrinogenemia may encounter bleeding or thrombosis contingent upon

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the specific sequence variant present [5]. Furthermore, increasing evidence indicates a correlation between non-O blood groups and venous thromboembolism (VTE) [6,7]. This evaluation excludes acquired thrombophilia, such as APS, and concentrates only on the most prevalent hereditary thrombophilia.

French recommendations advise against doing a routine fundamental thrombophilia screening after an initial episode of venous thromboembolism (VTE) [8], particularly for those over 50, regardless of whether the thrombosis is triggered. Consequently, it is recommended to conduct inherited thrombophilia testing in individuals experiencing their initial incident of unprompted proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) prior to the age of 50, particularly those with a first-degree family history of thrombosis; in patients with recurrent venous thromboembolism (VTE) (defined as a minimum of a single case of proximal DVT or PE and at least one unprompted segment before age 50); or in patients presenting with unprovoked VTE at atypical locations.

When testing for inherited thrombophilia is warranted, it is recommended to investigate the following abnormalities: deficiencies in antithrombin (AT), protein C (PC), or protein S (PS), as well as the presence of the factor V Leiden (FVL) variant (HGVS nomenclature: F5 c.1601G>A) and the prothrombin G20210A variant (HGVS: F2 c.*97G>A) within three to six months post-VTE diagnosis [8]. In instances of verified natural inhibitor deficiency (AT, PC, and PS), the deficiency type is delineated using supplementary plasma assays, potentially including genotyping (see to Section 2) [9]. Genotyping and familial assessment may assist after a diagnosis of thrombogenic mutations that are not linked to overt plasmatic inhibitor deficits and in counseling for recessive forms, for instance [10,11].

The management of VTE relies on anticoagulant administration for a duration that varies according to many parameters. Direct oral anticoagulants (DOACs), available for more than a decade, include dabigatran, which inhibits thrombin, and apixaban, rivaroxaban, and edoxaban, which inhibit factor Xa (FXa) [12]. Direct oral anticoagulants (DOACs) have shown non-inferiority to vitamin K antagonists (VKAs) in the management of acute symptomatic venous thromboembolism (VTE), while also exhibiting decreased risks of significant bleeding (MANSOOR et al., 2021). They are administered orally, exhibit a fast start of anticoagulation, and do not need regular monitoring. Several years before, the use of DOACs surged as recommendations favored them over VKAs [13,14].

This study seeks to delineate the appropriate thrombophilia tests for patients undergoing direct oral anticoagulant treatment, while also reviewing the existing evidence on the effectiveness of direct oral anticoagulant therapy in individuals with hereditary thrombophilia.

Hereditary Thrombophilia

The incidence and thromboembolic risk of a first thrombosis episode or recurrence are contingent upon the kind of thrombophilia (severe or non-severe), as shown in Table 1 [15-17]. Genetic and environmental factors combine to induce venous thrombosis. Combined abnormalities, including the SERPINC1 variation and F5 Leiden cis segregation, are linked to an elevated risk of thrombosis [18]. Frequently chosen gene variations may significantly interact with infrequent mutations, resulting in potentially life-threatening diseases when coupled with uncommon, severe mutations [19]. FVL was first documented in 1994 [20]. This arises from the substitution of guanine with adenosine at position 1601 (formerly 1691) of the F5 gene. Arginine (Arg) at position 534 (formerly 506) of coagulation cofactor V is changed by glutamine (Glu). Activated protein C (APC) suppresses factor Va by cleaving at Arg 334 (formerly 306), 534 (formerly 506), and 707 (formerly 679). Consequently, FVL exhibits resistance to APC inactivation, leading to a gain in function of FVa [21,22].

The inheritance of FVL is autosomal dominant. FVL heterozygosity is the predominant prothrombotic gene variation among the Caucasian population, exhibiting a frequency of roughly 5%, with a range of 3 to 7%, with a positive gradient from southern to northern Europe. FVL heterozygosity occurs in the United States, with an average prevalence of 5% in the general population. The prevalence is lower among Black Americans Africans (1%) and Asians (0.5%) [1]. The prevalence increases to 20% in non-selected VTE patients. Homozygosity for FVL is seen in roughly 1 in 1000 persons within the general population and 1%

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of non-selected VTE patients. The risk of VTE rises around fivefold in heterozygous carriers and tenfold in homozygous carriers [23].

The intronic alteration c.*97G>A (formerly G20210A) of the F2 gene is situated downstream of the coding sequence, inside the 3' untranslated region (3' UTR). It is inside a functional zone that the maturation of messenger RNAs is conditioned. This variation enhances cleavage and maturation efficiency, leading to the accumulation of mature mRNA in the cytoplasm and an augmentation of protein synthesis [24]. This mechanism elucidates the substantial correlation of the variation with around 30% elevated levels of FII in heterozygous individuals. This increase in concentration may elucidate the variant's effect on thrombin production and its associated risk of thrombosis [25]. The F2 C.*97G>A variation, less frequent than FVL, is the second-most prevalent hereditary thrombophilia, occurring in around 2% of the European population, with an increasing gradient from south to north. It is less common among individuals from Africa and Asia. The inheritance of the F2 C.*97G>A mutation is autosomal dominant. This variant heterozygosity is associated with an almost twofold heightened risk of a first venous thromboembolism (VTE) occurrence, while it has not consistently shown an elevated risk of recurrent VTE [1].

The clinical phenotype linked to AT deficiency is diverse [26]. Type I antithrombin deficiency is often severe when there is a considerable decrease in antithrombin plasma concentration. In type II, heterogeneity is more significant. Some SERPINC1 variations, such as IIRS, p.Arg425del, or structural variants, produce clinical symptoms as severe as type I deficiency due to a negative dominant impact. Conversely, several polymorphisms have a modest functional impact and are linked to a reduced risk of thrombosis, as shown by the Cambridge II variant. HBS deficiency was once linked to a reduced risk of thrombosis. Recent studies indicate variability in thrombosis risk within the HBS group, with some variations, such as the Budapest III variant, exhibiting thrombotic characteristics comparable to type I defects, even in cases of heterozygous deficiency [26]. Homozygous AT deficiencies are very uncommon, since they often result in lethality prior to birth, and are mostly seen in type IIHBS deficits or other comparatively less deleterious variations. Genotyping of SERPINC1 does not account for all constitutional abnormalities of AT; few hereditary AT deficits are attributed to glycosylation anomalies within the framework of congenital disorders of glycosylation (CDG) syndrome [27].

PC is a vitamin K-dependent plasma glycoprotein produced by the liver as a zymogen of serine protease. Prothrombin is triggered by thrombin. The process is augmented by the complex created by thrombin and thrombomodulin, together with the binding of protein C to its endothelium receptor. Activated protein C (APC) limits thrombin production by proteolytically inactivating the coagulation cofactors FVa and FVIIIa. The PC route is crucial in modulating the thrombotic process, particularly in microcirculation, where the interaction between proteins and the endothelium is vital.

The most prevalent condition is heterozygous PC deficiency. Individuals with full protein C deficiency (homozygous) or those exhibiting very low plasma protein C levels provide a more severe clinical manifestation, sometimes shown by purpura fulminans in neonates, a potentially lethal disease marked by microvascular thrombosis and epidermal necrosis [28,29]. Prothrombin deficiency increases the risk of venous thromboembolism. Di Minno et al. [16] conducted a meta-analysis of observational data, revealing that the relative risk of a first episode of venous thromboembolism (VTE) linked to protein C deficiency was 7, whereas the risk of recurrence was 3 [16]. The findings are likely imprecise, since they were not derived from research including PROC genotypes [11].

Laboratory Assessment for Hereditary Thrombophilia in Patients on Direct Oral Anticoagulants

Biological Assessment of Hereditary Thrombophilia

The identification of FVL was originally predicated on plasma testing for APC resistance. Due to insensitivity and insufficient information on genetic status, molecular diagnosis is currently recommended as the primary test [36-38]. The identification of the G20210A variation of F2 is also grounded in molecular biology. These studies are unaffected by the presence of therapy and may be conducted in patients receiving

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DOACs. As APC resistance testing is no longer advised for detecting FVL, the impact of DOACs on this assessment is not elaborated upon in this study.

Screening for hereditary deficits of natural anticoagulants (protein C, protein S, and antithrombin) relies on functional assays that evaluate anticoagulant activity to identify both quantitative and qualitative abnormalities. Screening for antithrombin deficiency relies on chromogenic assays that evaluate heparin cofactor activity in inhibiting factor Xa or factor IIa. Should a decline be seen without an explicable acquired cause, the measurement of antithrombin antigen will indicate a quantitative or qualitative deficit [39,40]. Clot-based anticoagulant activity testing for PC and PS can identify all deficiency types. Numerous variables may disrupt these tests (biological parameters, such as FVIII levels and medications); thus, they are rarely consistently used as primary assays [41-43]. Nonetheless, they are essential for identifying type IIb PC and type II PS impairments. The diagnosis of PC deficits includes a chromogenic test that evaluates PC enzymatic activity and antigenic tests. The diagnosis of PS deficiency is confirmed by the measurement of PS-free antigen. Genotyping aids in the diagnosis of qualitative antithrombin deficiency and its related thrombotic risk. It may be beneficial to verify PC or PS deficiencies. The methods and locations for genotyping are not addressed here, since DOACs do not impact molecular biology [44,45].

Due to the temporary alterations in AT, PC, and PS seen during the acute phase of thrombosis, it is advisable to do thrombophilia testing within three to six months after a VTE episode [46-52]. Nonetheless, the outcomes may influence the length of therapy. Consequently, thrombophilia testing may be conducted while the patient is on anticoagulant therapy. For each inhibitor, we outline the documented interferences of DOACs in the assays used to identify hereditary deficits and the outcomes of DOAC neutralization for thrombophilia assessment.

Antithrombin

The inhibitory action of AT is often evaluated by quantifying residual FXa or FIIa activity by the addition of a surplus of the relevant enzyme to the test plasma. In these tests, FXa or thrombin is inhibited not only by AT but also by DOACs, which accounts for the overestimation of AT's inhibitory effect. FXa inhibition methods are influenced by rivaroxaban, apixaban, and edoxaban, whereas FIIa inhibition methods are influenced by dabigatran. The overestimation is contingent upon the dosage and changes according to the specific DOACs and reagents used. In tests conducted with DOAC-spiked plasma, several assays remained unaffected at low DOAC concentrations. Reported increases in AT activity include 12% per 200 ng/mL of dabigatran using Stachrom ATIII, 13% per 100 ng/mL of apixaban with HemosIL, 3% per 100 ng/mL of edoxaban with Innovance AT, and 9% per 100 ng/mL of rivaroxaban with Coamatic AT LR [38,47,49,53]. No substantial effect was seen with the Innovance AT reagent when the rivaroxaban plasma concentration was below 100 ng/mL [41]. Dabigatran concentrations below 100 ng/mL seemed to not affect FIIa-based AT activity as assessed using the Stachrom ATIII reagent [52,54,55]. The statistical assessment of the lack of DOACs' effect on an assay was varied.

The majority of experiments were performed on pooled normal plasma supplemented with varying doses of DOACs [56]. Some researchers utilized plasma from patients undergoing treatment with direct oral anticoagulants (DOACs) and juxtaposed the findings with those derived from unaffected assays, such as results from FIIa-based assays for patients receiving anti-Xa DOACs or contrasted the results with baseline antithrombin (AT) levels prior to the initiation of DOAC therapy [42,43]. The findings of one ex vivo investigation contrasted with the data obtained from normal pooled spiking plasma. Favresse et al. [57] detected no substantial interference of dabigatran in the measurement of AT activity using anti-IIa based assays. This observation may be elucidated by the reduced median concentration of dabigatran in these individuals (73.5 ng/mL).

Protein C

Clot-based tests for protein C depend on the suppression of clot formation subsequent to protein C activation. Regardless of the method used to initiate coagulation, whether by activated partial thromboplastin time (aPTT) or Russell's viper venom (RVV) tests, factor Xa (FXa) and factor IIa (FIIa)

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play a crucial role in clot formation. The extension of clotting time correlates with the concentration of PC in the plasma sample. Any Direct Oral Anticoagulant (DOAC) may influence these tests, resulting in an overestimation of the anticoagulant activity of prothrombin complex, hence potentially obscuring a deficient status [41,46-51,58].

An overestimation of the anticoagulant action of PC is dose-dependent with apixaban and rivaroxaban [49,58]. A 4% rise in PC activity per 100 ng/mL of apixaban has been shown using Staclot PC (clot-based assay) [49]. The sensitivity of PC clot-based tests to DOACs varied according on the specific medications and reagents used. The overestimation was lower with apixaban compared to rivaroxaban [58]. The PC Coag test exhibited lower sensitivity to apixaban compared to Staclot Protein C [49]. No substantial effect of DOACs was seen at low levels of dabigatran (<100 ng/mL) and even for elevated quantities of apixaban (>750 ng/mL), edoxaban (>276 ng/mL), and rivaroxaban (>222 ng/mL) when using the PC reagent from Siemens [41,51].

The majority of experiments were performed on pooled normal plasma supplemented with varying doses of DOACs. In contrast to AT, all varieties of DOACs affected PC clot-based tests. No comparable alternative technique can yet be suggested. Consequently, illustrating the impact of DOACs using plasma from patients undergoing DOAC treatment may be more challenging. Significantly, there is a paucity of evidence about the impact of DOACs on clot-based PC assays compared to AT activity or clot-based PS tests. The assessment of antigenic PC or functional PC using a chromogenic approach remained unaltered by DOACs. Numerous studies have evaluated chromogenic tests using spiking pooled normal plasma [40-42,45,47,49-52,54-57,59].

Protein S

Functional (clot-based) PS tests rely on prothrombin time (PT), activated partial thromboplastin time (aPTT), or Russell's viper venom (RVV). They depend on the suppression of clot formation by PS in conjunction with APC, FXa, and FIIa, which are all implicated in clot formation, regardless of the test used. The extension of clotting time correlates with the concentration of PS in the plasma sample. Samples containing DOAC will extend the clotting time, resulting in an overestimation of PS activity and the possibility of overlooking a deficit [40,41,46,47,49,50-55,58-62].

A dose-dependent exaggeration of PS anticoagulant efficacy was reported with dabigatran, apixaban, and rivaroxaban [40,52,58]. A 15% increase in PS activity per 100 ng/mL of rivaroxaban was seen using Staclot PS (clot-based assay) [54]. The sensitivity of PS clot-based tests to DOACs differed according on the specific medications and reagents used. The effects of DOACs were documented at low levels of dabigatran and rivaroxaban [41,51,55]. The overestimation was lower with apixaban compared to rivaroxaban [58]. The influence of DOACs seemed to be more significant on PS clot-based tests using PT or RVV activation compared to aPTT-based assays [63].

The majority of experiments were performed on pooled normal plasma supplemented with varying doses of DOACs. Unlike AT, all categories of DOACs affect PS clot-based tests. No comparable alternative technique can be suggested. Consequently, evaluating the influence of DOACs on plasma from treated individuals is more challenging. Maryamchik et al. compared the average PS functional activity with the average free PS Ag in 32 patients administered rivaroxaban (145 ng/mL; range 23 to 349 ng/mL) and in 40 patients administered apixaban (139.8 ng/mL; range 27.5 to 652.0) [60,62]. Rivaroxaban artificially increased PS activity, leading to misdiagnoses of PS insufficiency, but in individuals on apixaban, functional PS activity did not substantially vary from free PS antigen levels. Additionally, low free PS Ag was seen in 3 out of 40 (8%) individuals in this trial, and in these three instances, PS activity was also reduced after apixaban therapy. These findings align with Gosselin et al., who showed apixaban interference only at doses beyond 471 ng/mL [41]. Hillarp et al. reported a 13% increase in PS activity at low dosages of apixaban (<100 ng/mL) [49]. Mani et al. further used plasma from individuals treated with rivaroxaban. The findings were compared to baseline levels of PS assessed prior to the initiation of DOAC therapy [42].

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Immunologic PS testing is often assessed using ELISA-based methods or latex-particle agglutination assays. The assessment of antigenic free PS is unaffected by DOACs. Thrombophilia tests may be considerably influenced by little quantities of DOACs. Their effects are contingent upon the medication, concentration, methodological testing, and reagents used. Antithrombotic activity may be assessed using either FXa- or FIIa-based assays, depending upon the specific target of the direct oral anticoagulants (DOACs). Apixaban seems to have less interference than rivaroxaban for PC and PS. Clot-based tests for PC may exhibit reduced sensitivity to DOACs, necessitating confirmation of testing at low doses for each reagent.

Neutralization of Direct Oral Anticoagulants

Multiple techniques were suggested to mitigate the influence of residual DOACs on coagulation tests. It has been recommended that individuals with low thromboembolic risk may miss one dose for once-daily fixed-dosage regimens or two doses for twice-daily fixed-dose regimens of DOAC consumption. Nonetheless, with the exception of apixaban, even the trough levels of DOACs may considerably influence thrombophilia tests. Consequently, to get precise findings, hemostasis testing should ideally be conducted four days after the cessation of DOAC medication; however, this is not endorsed from a therapeutic perspective. Transitioning from DOACs to low-molecular-weight heparin for a temporary duration may serve as an option when testing is required. DOAC-insensitive assays have been established for lupus anticoagulant testing; however, such assays are not accessible for hereditary thrombophilia testing. Targeted reversal agents, like idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban, have been formulated; however, they are costly and have not yet been used as standard reagents in diagnostic labs [64,65]. Ciraparantag is undergoing clinical testing as a universal reversal drug for both factor IIa and anti-Xa inhibitors. Nonetheless, none of these methods is perfect, and a straightforward solution to address the issue is to eliminate DOAC from the plasma sample without affecting its coagulation properties.

The method to eliminate this interference is now accessible with the introduction of adsorbent agents capable of extracting DOAC from a plasma sample. Two devices use activated charcoal. DOAC-Stop® was the first device designed to eliminate DOACs from a plasma sample. A comparable product, DOAC remove®, is also an absorbent tablet designed for plasma application. The manufacturer stipulates that one tablet is to be added per 1 mL of plasma and stirred for 5 to 10 minutes. Following centrifugation, the plasma is decanted to conduct coagulation tests. Activated charcoals (AC) are porous carbon materials characterized by a substantial internal surface area. The majority are commercially manufactured items used in industry or medicines. Medical grade activated charcoal, often coated with porous hydrophilic polymers, has enhanced biocompatibility with blood but may possess a diminished ability for adsorbing drug molecules. Due to the varying quality of ACs provided by chemical suppliers, it is improbable that they may be used interchangeably. Recently, filters coated with absorbent materials, such as DOAC-Filter®, have been created [66]. DOAC-Filter® is a pre-assembled single cartridge that has a solid phase. The concept of solid-phase extraction relies on a noncovalent binding mechanism. The hydrophilic-hydrophobic equilibrium of the solid phase has been ascertained to selectively capture DOACs. This gadget is user-friendly and prevents the transfer of residues that might compromise the measurement. A little volume reduction occurs post-centrifugation. The fundamental criteria include sufficient binding capacity to accommodate the maximum concentrations of DOACs anticipated in clinical settings, while ensuring no interference with testing in plasma devoid of DOACs. All three procedures may neutralize DOACs in plasma samples from individuals undergoing treatment. Furthermore, partial reversal was seen in 2 out of 21 patients treated with DOAC Remove® and in 1 out of 18 patients treated with DOAC-Filter® [66]. The partial reversal did not consistently pertain to individuals exhibiting the highest plasma DOAC levels.

Multiple research groups have investigated the effects of plasma therapy with these reversal agents on AT, PC, and PS levels. The effect was evaluated using plasma samples from untreated healthy persons [45,57,58,66,67] or assessment techniques unaffected by DOACs, including an anti-FIIa-based test to detect AT activity in patients receiving apixaban [44] or PC chromogenic assays [45,56,67]. Monteyne et al. showed a notable reduction in PC amidolytic activity, although this was seen just with the administration of two tablets of DOAC-Stop®, which did not correlate with a clinically meaningful impact [67]. They also reported a reduction in PS levels (free PS Ag) in healthy persons with both DOAC-reversal drugs, as

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determined by the Wilcoxon rank test. The clinical effect was not specified, however the reduction was minimal [67].

Research on DOAC reversal used plasma from individuals undergoing DOAC treatment. The study indicated a reduction in inhibitor levels following plasma treatment with AC devices and validated the interference noted with normal plasma spiked with DOACs: interference in the clot-based assessment of PC [58] and PS [58,63], as well as interference of anti-Xa DOACs in the evaluation of AT activity using FXa-based assays [44]. Smock et al. also noted a discrepancy in the interference of dabigatran in PS clot-based tests dependent on the technique used (RVV- vs aPTT-based) [63].

The influence of DOACs may lead to an overestimation of findings, perhaps obscuring a deficit. A low measured level of AT, PC, or PS indicates a deficit, since it may signify a more significant underlying problem than what is apparent. Nonetheless, when the measured amount is normal, it becomes more challenging to ascertain if a shortage is concealed. Consequently, while a reduction in anticoagulant levels is seen with the neutralization of DOACs, it may be challenging to ascertain the full normalization of the results after DOAC reversal. Even at concentrations below the limit of quantification, DOAC may still disrupt some tests and obscure a deficit. Two kinds of tests are available for AT testing that can determine the efficacy of DOAC reversal. Zabcyck et al. examined 130 patients receiving DOACs for thromboembolism: 49 on rivaroxaban, with a concentration of 104 ng/mL (IQR, 45–334 ng/mL); 54 on apixaban, with a concentration of 93.5 ng/mL (IQR, 64–145 ng/mL); and 27 on dabigatran, with a concentration of 71 ng/mL (IQR, 48–144 ng/mL) [44]. Ten individuals had AT deficiency identified by an anti-IIa-based assay and then verified via genetic testing. All subjects received anti-FXa direct oral anticoagulants (DOACs). Utilizing the anti-FXa based test, AT activity was reduced only in three cases. The DOAC-Stop® medication led to an increase in the number of patients exhibiting AT activity below reference levels, as measured by the FXa-based test, from 3 to 10 individuals. Consequently, DOAC-Stop® rectified the identification of the seven false-negative patients with antithrombin deficiency, four of whom were treated with apixaban and three with rivaroxaban. Favre et al. examined 47 individuals administered DOACs for whom thrombophilia testing was mandated [58]. Inherited thrombophilia was assessed in 12 individuals receiving apixaban and 9 patients receiving rivaroxaban. They analyzed the clot-based activities of PC and PS in relation to patient Ag levels and reported a dose-dependent overestimation caused by DOACs. Subsequent to the ex vivo treatment of plasma with DOAC Remove®, the overestimation of functional PC and PS reverted to levels consistent with Ag measurements. Furthermore, a reduction in PS activity from 92% to 53% in a single sample indicated a genuine PS deficit, corroborated by the molecular analysis of the PROS1 gene.

The adsorbent method proved to be an efficient and straightforward approach to mitigate the influence of DOACs in coagulation tests, hence enhancing the interpretation of thrombophilia screening tests in individuals on DOAC therapy. In contrast to particular reversal medicines like idarucizumab or andexanet alfa, these methods have the benefits of eliminating all categories of DOACs while being straightforward, cost-effective, and readily available. A cutoff ensuring the lack of interference must be set using DOAC-treated plasma. This cutoff must be tailored to the reagent used and the patient's therapy. When clot-based assays are not used to evaluate the existence of PC or PS deficits, the potential for overlooking a qualitative deficiency must be communicated to the doctors.

Conclusions

Our understanding of hereditary thrombophilia has significantly advanced in recent decades, resulting in enhanced identification and characterization of thrombophilia and its related venous thromboembolism risk. The most uncommon thrombophilia deficiencies, such as antithrombin (AT), protein C (PC), and protein S (PS) deficiencies, are linked to a severe phenotype, in contrast to the more prevalent genetic variations like factor V Leiden (FVL) and prothrombin G20210A (F2 C.*97G>A). The extensive use of direct oral anticoagulants (DOACs) for venous thromboembolism (VTD) has introduced new challenges regarding hereditary thrombophilia. DOACs may influence thrombophilia tests, perhaps leading to false-negative findings. Thrombophilia tests may be considerably influenced by little quantities of DOACs. Their

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effects are contingent upon the medication, concentration, methodological testing, and reagents used. Antithrombotic activity may be assessed using either FXa- or FIIa-based assays, depending upon the specific target of the direct oral anticoagulant (DOAC). Apixaban seems to have less interference than rivaroxaban for PC and PS. Clot-based tests for PC would exhibit reduced sensitivity to DOACs, necessitating confirmation of testing at low doses for each reagent.

Consequently, up-to-date therapy information is essential to avoid misclassification and ensuing clinical ramifications. Furthermore, the adsorbent method seems to be an efficient and straightforward approach to mitigate the disruptive effects of DOACs in coagulation assays, hence enhancing the comprehension of thrombophilia examinations in patients on DOACs. In conclusion, testing for hereditary thrombophilia in individuals on DOAC treatment should be conducted at a specialized laboratory for thrombophilia. Severe thrombophilia, linked to an elevated risk of thrombosis repetition, is uncommon and inadequately documented in clinical research. The literature presents positive results about the effectiveness and safety of DOACs in this context. Nonetheless, the risk of thrombosis differs with deficits, therefore more information, including well-defined thrombophilia individuals, would be beneficial to validate the existing results.

References

Mannucci, P.M.; Franchini, M. Classic Thrombophilic Gene Variants. Thromb. Haemost. 2015, 114, 885–889.
Fekih-Mrissa, N.; Klai, S.; Mrad, M.; Zaouali, J.; Sayeh, A.; Nsiri, B.; Gritli, N.; Mrissa, R. Role of Methylenetetrahydrofolate Reductase A1298C Polymorphism in Cerebral Venous Thrombosis. Blood Coagul. Fibrinolysis 2013, 24, 118–119.
Simioni, P.; Tormene, D.; Tognin, G.; Gavasso, S.; Bulato, C.; Iacobelli, N.P.; Finn, J.D.; Spiezia, L.; Radu, C.; Arruda, V.R. X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua). N. Engl. J. Med. 2009, 361, 1671–1675.
Casini, A.; Undas, A.; Palla, R.; Thachil, J.; de Moerloose, P. Subcommittee on Factor XIII and Fibrinogen Diagnosis and Classification of Congenital Fibrinogen Disorders: Communication from the SSC of the ISTH. J. Thromb. Haemost. JTH 2018, 16, 1887–1890.
Simurda, T.; Zolkova, J.; Kolkova, Z.; Loderer, D.; Dobrotova, M.; Skornova, I.; Brunclíkova, M.; Grendar, M.; Lasabova, Z.; Stasko, J.; et al. Comparison of Clinical Phenotype with Genetic and Laboratory Results in 31 Patients with Congenital Dysfibrinogenemia in Northern Slovakia. Int. J. Hematol. 2020, 111, 795–802.
Wu, O.; Bayoumi, N.; Vickers, M.A.; Clark, P. ABO(H) Blood Groups and Vascular Disease: A Systematic Review and Meta-Analysis. J. Thromb. Haemost. JTH 2008, 6, 62–69.
Trégouët, D.-A.; Heath, S.; Saut, N.; Biron-Andreani, C.; Schved, J.-F.; Pernod, G.; Galan, P.; Drouet, L.; Zelenika, D.; Juhan-Vague, I.; et al. Common Susceptibility Alleles Are Unlikely to Contribute as Strongly as the FV and ABO Loci to VTE Risk: Results from a GWAS Approach. Blood 2009, 113, 5298–5303.
Sanchez, O.; Benhamou, Y.; Bertoletti, L.; Constant, J.; Couturaud, F.; Delluc, A.; Elias, A.; Fischer, A.-M.; Frappé, P.; Gendron, N.; et al. Recommendations of good practice for the management of thromboembolic venous disease in adults. Short version. Rev. Mal. Respir. 2019, 36, 249–283.
Thrombophilie Biologique: Propositions GFHT 2020—Groupe d'etude Sur l'hemostase et La Thrombose.
Alhenc-Gelas, M.; Plu-Bureau, G.; Horellou, M.H.; Rauch, A.; Suchon, P. GEHT genetic thrombophilia group PROS1 Genotype Phenotype Relationships in a Large Cohort of Adults with Suspicion of Inherited Quantitative Protein S Deficiency. Thromb. Haemost. 2016, 115, 570–579.
Alhenc-Gelas, M.; Plu-Bureau, G.; Mauge, L.; Gandrille, S.; Présot, I. GFHT Study Group on Genetic Thrombophilia Genotype-Phenotype Relationships in a Large French Cohort of Subjects with Inherited Protein C Deficiency. Thromb. Haemost. 2020, 120, 1270–1281.
van Es, N.; Coppens, M.; Schulman, S.; Middeldorp, S.; Büller, H.R. Direct Oral Anticoagulants Compared with Vitamin K Antagonists for Acute Venous Thromboembolism: Evidence from Phase 3 Trials. Blood 2014, 124, 1968–1975.
Smadja, D.-M.; Gendron, N.; Sanchez, O. Comment et chez qui faut-il surveiller les traitements anticoagulants? Rev. Mal. Respir. 2019, S076184251930213X.
Konstantinides, S.V.; Meyer, G.; Becattini, C.; Bueno, H.; Geersing, G.-J.; Harjola, V.-P.; Huisman, M.V.; Humbert, M.; Jennings, C.S.; Jiménez, D.; et al. 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration with the European Respiratory Society (ERS). Eur. Heart J. 2019, 40, 3453–3455.
Rosendaal, F.R. Venous Thrombosis: The Role of Genes, Environment, and Behavior. Hematol. Am. Soc. Hematol. Educ. Program 2005, 307–313.
Di Minno, M.N.D.; Ambrosino, P.; Ageno, W.; Rosendaal, F.; Di Minno, G.; Dentali, F. Natural Anticoagulants Deficiency and the Risk of Venous Thromboembolism: A Meta-Analysis of Observational Studies. Thromb. Res. 2015, 135, 923–932.
Simone, B.; De Stefano, V.; Leoncini, E.; Zacho, J.; Martinelli, I.; Emmerich, J.; Rossi, E.; Folsom, A.R.; Almawi, W.Y.; Scarabin, P.Y.; et al. Risk of Venous Thromboembolism Associated with Single and Combined Effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate Reductase C677T: A Meta-Analysis Involving over 11,000 Cases and 21,000 Controls. Eur. J. Epidemiol. 2013, 28, 621–647.

Journal of Ecohumanism
2024
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van Boven, H.H.; Vandenbroucke, J.P.; Brie¨t, E.; Rosendaal, F.R. Gene-Gene and Gene-Environment Interactions Determine Risk of Thrombosis in Families With Inherited Antithrombin Deficiency. Blood 1999, 94, 2590–2594.
Gemmati, D.; Longo, G.; Franchini, E.; Araujo Silva, J.; Gallo, I.; Lunghi, B.; Moratelli, S.; Maestri, I.; Serino, M.L.; Tisato, V. Cis-Segregation of c.1171C>T Stop Codon (p.R391*) in SERPINC1 Gene and c.1691G>A Transition (p.R506Q) in F5 Gene and Selected GWAS Multilocus Approach in Inherited Thrombophilia. Genes 2021, 12, 934.
Bertina, R.M.; Koeleman, B.P.C.; Koster, T.; Rosendaal, F.R.; Dirven, R.J.; de Ronde, H.; van der Velden, P.A.; Reitsma, P.H. Mutation in Blood Coagulation Factor V Associated with Resistance to Activated Protein C. Nature 1994, 369, 64–67.
Dahlbäck, B.; Carlsson, M.; Svensson, P.J. Familial Thrombophilia Due to a Previously Unrecognized Mechanism Characterized by Poor Anticoagulant Response to Activated Protein C: Prediction of a Cofactor to Activated Protein C. Proc. Natl. Acad. Sci. USA 1993, 90, 1004–1008.
Koster, T.; Rosendaal, F.R.; de Ronde, H.; Briët, E.; Vandenbroucke, J.P.; Bertina, R.M. Venous Thrombosis Due to Poor Anticoagulant Response to Activated Protein C: Leiden Thrombophilia Study. Lancet Lond. Engl. 1993, 342, 1503–1506.
Lijfering, W.M.; Middeldorp, S.; Veeger, N.J.G.M.; Hamulyák, K.; Prins, M.H.; Büller, H.R.; van der Meer, J. Risk of Recurrent Venous Thrombosis in Homozygous Carriers and Double Heterozygous Carriers of Factor V Leiden and Prothrombin G20210A. Circulation 2010, 121, 1706–1712.
Poort, S.R.; Rosendaal, F.R.; Reitsma, P.H.; Bertina, R.M. A Common Genetic Variation in the 3′-Untranslated Region of the Prothrombin Gene Is Associated with Elevated Plasma Prothrombin Levels and an Increase in Venous Thrombosis. Blood 1996, 88, 3698–3703.
Egeberg, O. Inherited Antithrombin Deficiency Causing Thrombophilia. Thromb. Diath. Haemorrh. 1965, 13, 516–530.
Alhenc-Gelas, M.; Plu-Bureau, G.; Hugon-Rodin, J.; Picard, V.; Horellou, M.-H. GFHT study group on Genetic Thrombophilia Thrombotic Risk According to SERPINC1 Genotype in a Large Cohort of Subjects with Antithrombin Inherited Deficiency. Thromb. Haemost. 2017, 117, 1040–1051.
de la Morena-Barrio, M.E.; Martínez-Martínez, I.; de Cos, C.; Wypasek, E.; Roldán, V.; Undas, A.; van Scherpenzeel, M.; Lefeber, D.J.; Toderici, M.; Sevivas, T.; et al. Hypoglycosylation Is a Common Finding in Antithrombin Deficiency in the Absence of a SERPINC1 Gene Defect. J. Thromb. Haemost. JTH 2016, 14, 1549–1560.
Branson, H.; Marble, R.; Katz, J.; Griffin, J. Inherited Protein C Deficiency and Coumarin-Responsive Chronic Relapsing Purpura Fulminans in a Newborn Infant. Lancet 1983, 322, 1165–1168.
Marlar, R.A.; Montgomery, R.R.; Broekmans, A.W. Diagnosis and Treatment of Homozygous Protein C Deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. J. Pediatr. 1989, 114, 528–534.
Griffin, J.H.; Evatt, B.; Zimmerman, T.S.; Kleiss, A.J.; Wideman, C. Deficiency of Protein C in Congenital Thrombotic Disease. J. Clin. Investig. 1981, 68, 1370–1373.
Broekmans, A.W.; Veltkamp, J.J.; Bertina, R.M. Congenital Protein C Deficiency and Venous Thromboembolism. A Study of Three Dutch Families. N. Engl. J. Med. 1983, 309, 340–344.
Linssen, M.; Mohamed, M.; Wevers, R.A.; Lefeber, D.J.; Morava, E. Thrombotic Complications in Patients with PMM2-CDG. Mol. Genet. Metab. 2013, 109, 107–111.
Alhenc-Gelas, M.; Canonico, M.; Morange, P.E.; Emmerich, J. Geht Genetic Thrombophilia Group Protein S Inherited Qualitative Deficiency: Novel Mutations and Phenotypic Influence. J. Thromb. Haemost. JTH 2010, 8, 2718–2726.
Bertina, R.M.; Ploos van Amstel, H.K.; van Wijngaarden, A.; Coenen, J.; Leemhuis, M.P.; Deutz-Terlouw, P.P.; van der Linden, I.K.; Reitsma, P.H. Heerlen Polymorphism of Protein S, an Immunologic Polymorphism Due to Dimorphism of Residue 460. Blood 1990, 76, 538–548.
Suchon, P.; Germain, M.; Delluc, A.; Smadja, D.; Jouven, X.; Gyorgy, B.; Saut, N.; Ibrahim, M.; Deleuze, J.F.; Alessi, M.C.; et al. Protein S Heerlen Mutation Heterozygosity Is Associated with Venous Thrombosis Risk. Sci. Rep. 2017, 7, 45507.
Recherche d'une thrombophilie biologique: Propositions du GFHT 2020. Rev. Francoph. Hémostase Thromb.
Alhenc-Gelas, M.; Mauge, L. Bilan de thrombophilie. Rev. Francoph. Lab. 2020, 2020, 26–33.
Hillarp, A.; Baghaei, F.; Fagerberg Blixter, I.; Gustafsson, K.M.; Stigendal, L.; Sten-Linder, M.; Strandberg, K.; Lindahl, T.L. Effects of the Oral, Direct Factor Xa Inhibitor Rivaroxaban on Commonly Used Coagulation Assays. J. Thromb. Haemost. JTH 2011, 9, 133–139.
Van Blerk, M.; Bailleul, E.; Chatelain, B.; Demulder, A.; Devreese, K.; Douxfils, J.; Jochmans, K.; Mullier, F.; Wijns, W.; Soumali, M.R.; et al. Influence of Dabigatran and Rivaroxaban on Routine Coagulation Assays. A Nationwide Belgian Survey. Thromb. Haemost. 2015, 113, 154–164.
Bonar, R.; Favaloro, E.J.; Mohammed, S.; Ahuja, M.; Pasalic, L.; Sioufi, J.; Marsden, K. The Effect of the Direct Factor Xa Inhibitors Apixaban and Rivaroxaban on Haemostasis Tests: A Comprehensive Assessment Using in Vitro and Ex Vivo Samples. Pathology 2016, 48, 60–71.
Gosselin, R.; Grant, R.P.; Adcock, D.M. Comparison of the Effect of the Anti-Xa Direct Oral Anticoagulants Apixaban, Edoxaban, and Rivaroxaban on Coagulation Assays. Int. J. Lab. Hematol. 2016, 38, 505–513.
Mani, H.; Hesse, C.; Stratmann, G.; Lindhoff-Last, E. Rivaroxaban Differentially Influences Ex Vivo Global Coagulation Assays Based on the Administration Time. Thromb. Haemost. 2011, 106, 156–164.
Rühl, H.; Reda, S.; Müller, J.; Oldenburg, J.; Pötzsch, B. Activated Factor X-Based versus Thrombin-Based Antithrombin Testing in Thrombophilia Workup in the DOAC Era. Thromb. Haemost. 2018, 118, 381–387.
Ząbczyk, M.; Natorska, J.; Kopytek, M.; Malinowski, K.P.; Undas, A. The Effect of Direct Oral Anticoagulants on Antithrombin Activity Testing Is Abolished by DOAC-Stop in Venous Thromboembolism Patients. Arch. Pathol. Lab. Med. 2021, 145, 99–104.

Journal of Ecohumanism
2024
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Exner, T.; Michalopoulos, N.; Pearce, J.; Xavier, R.; Ahuja, M. Simple Method for Removing DOACs from Plasma Samples. Thromb. Res. 2018, 163, 117–122.
Tripodi, A.; Padovan, L.; Testa, S.; Legnani, C.; Chantarangkul, V.; Scalambrino, E.; Ludovici, S.; Bassi, L.; Peyvandi, F. How the Direct Oral Anticoagulant Apixaban Affects Hemostatic Parameters. Results of a Multicenter Multiplatform Study. Clin. Chem. Lab. Med. 2015, 53, 265–273.
Douxfils, J.; Chatelain, C.; Chatelain, B.; Dogné, J.-M.; Mullier, F. Impact of Apixaban on Routine and Specific Coagulation Assays: A Practical Laboratory Guide. Thromb. Haemost. 2013, 110, 283–294.
Van Blerk, M.; Bailleul, E.; Chatelain, B.; Demulder, A.; Devreese, K.; Douxfils, J.; Jacquemin, M.; Jochmans, K.; Mullier, F.; Wijns, W.; et al. Influence of Apixaban on Commonly Used Coagulation Assays: Results from the Belgian National External Quality Assessment Scheme. Int. J. Lab. Hematol. 2017, 39, 402–408.
Hillarp, A.; Gustafsson, K.M.; Faxälv, L.; Strandberg, K.; Baghaei, F.; Fagerberg Blixter, I.; Berndtsson, M.; Lindahl, T.L. Effects of the Oral, Direct Factor Xa Inhibitor Apixaban on Routine Coagulation Assays and Anti-FXa Assays. J. Thromb. Haemost. JTH 2014, 12, 1545–1553.
Douxfils, J.; Chatelain, B.; Chatelain, C.; Dogné, J.-M.; Mullier, F. Edoxaban: Impact on Routine and Specific Coagulation Assays. A Practical Laboratory Guide. Thromb. Haemost. 2016, 115, 368–381.
Adcock, D.M.; Gosselin, R.; Kitchen, S.; Dwyre, D.M. The Effect of Dabigatran on Select Specialty Coagulation Assays. Am. J. Clin. Pathol. 2013, 139, 102–109.
Bonar, R.; Favaloro, E.J.; Mohammed, S.; Pasalic, L.; Sioufi, J.; Marsden, K. The Effect of Dabigatran on Haemostasis Tests: A Comprehensive Assessment Using in Vitro and Ex Vivo Samples. Pathology 2015, 47, 355–364.
Lindahl, T.L.; Baghaei, F.; Blixter, I.F.; Gustafsson, K.M.; Stigendal, L.; Sten-Linder, M.; Strandberg, K.; Hillarp, A. Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden Effects of the Oral, Direct Thrombin Inhibitor Dabigatran on Five Common Coagulation Assays. Thromb. Haemost. 2011, 105, 371–378.
Douxfils, J.; Mullier, F.; Loosen, C.; Chatelain, C.; Chatelain, B.; Dogné, J.-M. Assessment of the Impact of Rivaroxaban on Coagulation Assays: Laboratory Recommendations for the Monitoring of Rivaroxaban and Review of the Literature. Thromb. Res. 2012, 130, 956–966.
Kim, Y.A.; Gosselin, R.; Van Cott, E.M. The Effects of Dabigatran on Lupus Anticoagulant, Diluted Plasma Thrombin Time, and Other Specialized Coagulation Assays. Int. J. Lab. Hematol. 2015, 37, e81–e84.
Cox-Morton, S.; MacDonald, S.; Thomas, W. A Diagnostic Solution for Haemostasis Laboratories for Patients Taking Direct Oral Anticoagulants Using DOAC-Remove. Br. J. Haematol. 2019, 187, 377–385.
Favresse, J.; Lardinois, B.; Sabor, L.; Devalet, B.; Vandepapeliere, J.; Braibant, M.; Lessire, S.; Chatelain, B.; Jacqmin, H.; Douxfils, J.; et al. Evaluation of the DOAC-Stop® Procedure to Overcome the Effect of DOACs on Several Thrombophilia Screening Tests. TH Open Companion J. Thromb. Haemost. 2018, 2, e202–e209.
Favre, R.; Zia-Chahabi, S.; Talb, Y.; de Gunzburg, N.; Flaujac, C. Direct Oral Anticoagulant Neutralization by Activated Charcoal DOAC-Remove for Thrombophilia Screening. Blood Coagul. Fibrinolysis Int. J. Haemost. Thromb. 2021, 32, 356–358.
Gerotziafas, G.T.; Baccouche, H.; Sassi, M.; Galea, V.; Chaari, M.; Hatmi, M.; Samama, M.M.; Elalamy, I. Optimisation of the Assays for the Measurement of Clotting Factor Activity in the Presence of Rivaroxaban. Thromb. Res. 2012, 129, 101–103.
Maryamchik, E.; Van Cott, E.M. Apixaban Does Not Interfere With Protein S or Activated Protein C Resistance (Factor V Leiden) Testing Using APTT-Based Methods. Arch. Pathol. Lab. Med. 2020, 144, 1401–1407.
Mani, H.; Hesse, C.; Stratmann, G.; Lindhoff-Last, E. Ex Vivo Effects of Low-Dose Rivaroxaban on Specific Coagulation Assays and Coagulation Factor Activities in Patients under Real Life Conditions. Thromb. Haemost. 2013, 109, 127–136.
Maryamchik, E.; Rosenbaum, M.W.; Van Cott, E.M. Rivaroxaban Causes Missed Diagnosis of Protein S Deficiency but Not of Activated Protein C Resistance (Factor V Leiden). Arch. Pathol. Lab. Med. 2018, 142, 70–74.
MANSOOR, M., AWAN, T. M., & PARACHA, O. S. (2021). Predicting pro-environmental behaviors of green electronic appliances' users. International Journal of Business and Economic Affairs, 6(4), 175-186.
Smock, K.J.; Plumhoff, E.A.; Meijer, P.; Hsu, P.; Zantek, N.D.; Heikal, N.M.; Van Cott, E.M. Protein S Testing in Patients with Protein S Deficiency, Factor V Leiden, and Rivaroxaban by North American Specialized Coagulation Laboratories. Thromb. Haemost. 2016, 116, 50–57.
Jacquemin, M.; Toelen, J.; Schoeters, J.; van Horenbeeck, I.; Vanlinthout, I.; Debasse, M.; Peetermans, M.; Vanassche, T.; Peerlinck, K.; van Ryn, J.; et al. The Addition of Idarucizumab to Plasma Samples Containing Dabigatran Allows the Use of Routine Coagulation Assays for the Diagnosis of Hemostasis Disorders. J. Thromb. Haemost. JTH 2015, 13, 2087–2092.
Favaloro, E.J.; Gilmore, G.; Arunachalam, S.; Mohammed, S.; Baker, R. Neutralising Rivaroxaban Induced Interference in Laboratory Testing for Lupus Anticoagulant (LA): A Comparative Study Using DOAC Stop and Andexanet Alfa. Thromb. Res. 2019, 180, 10–19.
Sevenet, P.-O.; Cucini, V.; Hervé, T.; Depasse, F.; Carlo, A.; Contant, G.; Mathieu, O. Evaluation of DOAC Filter, a New Device to Remove Direct Oral Anticoagulants from Plasma Samples. Int. J. Lab. Hematol. 2020, 42, 636–642.
Monteyne, T.; De Kesel, P.; Devreese, K.M.J. Interference of DOAC Stop and DOAC Remove in the Thrombin Generation Assay and Coagulation Assays. Thromb. Res. 2020, 192, 96–99.

Journal of Ecohumanism
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التحديات في التشخيص المخبري للتخثر الوراثي: مراجعة متعمقة للقضايا الحالية والأساليب

الملخص

الخلفية :يتأثر مرض الانصمام الخثاري الوريدي (VTD) بعوامل خطر بيولوجية وطبية وبيئية متعددة، حيث يمثل التخثر الوراثي استعدادًا مكتسبًا أو وراثيًا للإصابة بالانصمام الوريدي .(VTE) تعقيد تحديد المرضى المناسبين لاختبارات التخثر الوراثي وتفسير النتائج يجعل إدارة الحالات السريرية أكثر صعوبة.

الطرق: تستعرض هذه المراجعة التخثر الوراثي التقليدي، بما في ذلك نقص مضادات التخثر الطبيعية والطفرات مثل طفرة العامل الخامس لايدن وطفرة البروثرومبين .G20210A وتبرز المراجعة أهمية التشخيص الجزيئي مقارنة بالاختبارات البلازمية التقليدية، خاصة في المرضى الذين يتلقون العلاج بمضادات التخثر الفموية المباشرة .(DOACs) كما تناقش توقيت اختبارات التخثر الوراثي ودور التنميط الجيني.

النتائج: تكشف النتائج أن وجود مضادات التخثر الفموية المباشرة يؤثر بشكل كبير على التحاليل المخبرية لتشخيص التخثر الوراثي. وتُظهر الاختبارات الوظيفية لمضادات الثرومبين والبروتين C والبروتين S تباينًا في الحساسية تجاهDOACs ، مما يؤدي إلى احتمالية ظهور نتائج سلبية كاذبة. تسلط المراجعة الضوء على أهمية تحييد تأثير DOACs قبل إجراء الاختبارات لضمان دقة النتائج، وتستعرض الأساليب الحديثة لإزالة تأثير DOACsباستخدام مواد ممتزة.

الخلاصة: أصبح التشخيص المخبري للتخثر الوراثي أكثر تحديًا بسبب الاستخدام الواسع لمضادات التخثر الفموية المباشرة. يعد الفهم المعمق لتأثير هذه الأدوية على الاختبارات ضروريًا لتشخيص دقيق وعلاج فعال. وتقترح المراجعة أن يتم إجراء تقييمات التخثر الوراثي في مختبرات متخصصة للمرضى الذين يتناولون DOACs لتحسين دقة التشخيص والنتائج السريرية.

الكلمات المفتاحية :التخثر الوراثي، الانصمام الوريدي، مضادات التخثر الفموية المباشرة، التشخيص المخبري، الاختبارات الجينية.