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FORUM

Primary prophylaxis of venous thromboembolic disease with direct oral anticoagulants in patients with severe inherited thrombophilia

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Abstract

Direct oral anticoagulants (DOACs) are widely used in several indications, but data on their efficacy and safety in individuals affected by severe inherited thrombophilia, yet without any personal history of thrombosis, is lacking. Severe inherited thrombophilia abnormalities, especially antithrombin deficiency, confer a higher risk of developing venous thromboembolism (VTE) than is the case in the general population. In this article, we propose primary prevention with low-dose DOACs for certain patients with severe inherited thrombophilia but without any personal history of VTE, while taking into consideration the type of thrombophilia, family history, comorbidities, and bleeding risk.

KEYWORDS
anticoagulants, antithrombin deficiency, apixaban, rivaroxaban, thrombophilia, venous thromboembolism

Essentials

- Direct oral anticoagulants (DOACs) are effective and safe in several indications.
- Recent data seem to support treatment of venous thromboembolism with DOACs in severe inherited thrombophilia.
- We suggest considering primary prophylaxis with low-dose DOACs in high-risk thrombophilia.
- Further research on safety and efficacy of DOACs in this indication is needed.

Direct oral anticoagulants (DOACs) have been extensively investigated and proven to be both effective and safe. As these agents are now widely available, they have become the antithrombotic treatment of choice for several indications, including primary and secondary stroke prevention in patients with nonvalvular atrial fibrillation and primary venous thromboembolism (VTE) prophylaxis following elective major orthopedic surgery. Additionally, DOACs are recommended for acute and prolonged treatment of VTE.

Nevertheless, little is known about DOACs' efficacy and safety in individuals with inherited thrombophilia that was demonstrated following genetic family screening, without any personal VTE history in the past. Inherited thrombophilia for which family screening may be performed comprises severe thrombophilia like protein C and S deficiency and antithrombin deficiency, in addition to less severe abnormalities like factor V Leiden and prothrombin G20210A mutations, either alone or in combination.

We recently decided to substitute a vitamin K antagonist (VKA) with a DOAC in a 52-year-old patient who had experienced multiple VTE episodes, including one unprovoked deep vein thrombosis (DVT) in 1985, when she was 17, which was complicated by

pulmonary embolism, with smoking and oral contraception identified as the sole risk factors at that time; one DVT in 1996 following a long-haul flight; and one DVT during pregnancy in 2002. The patient was diagnosed with antithrombin (AT) deficiency in 1997. Her AT level was estimated at 43% (normal range, 78%-130%), using a functional chromogenic assay. Genetic testing conducted later confirmed a type I deficiency (nonsense mutation c.1171C > T, p.Arg 391* in exon 5).

Our patient's daughter was born in 2003. Shortly after her birth, she underwent aortic coarctation surgery, which was complicated by cardiogenic shock and thrombus formation in the descending aorta and left subclavian artery. Considering her personal and family thrombosis history and in agreement with international guidelines,[1] she was referred to us for genetic screening in 2006, which revealed the same mutation in the AT gene as in her mother. Her AT level was measured at 42%, based on a functional chromogenic assay. To date, this patient has not presented with any further venous or arterial thrombotic events, in spite of not being administered any anticoagulant therapy. However, she has been advised to avoid contraceptives containing estrogen and was informed about the necessity of thromboprophylaxis in high-risk situations, such as surgery, pregnancy, or long-distance flights, as recommended in the literature.[1]

Overall, individuals with AT deficiency display a greater risk of developing VTE than the general population, their relative risk of developing a first VTE being the highest among all inherited thrombophilia,[2] and especially high compared to other conditions predisposing to arterial or venous thrombosis (Table 1). Notably, the risk of thrombosis associated with AT deficiency depends on the defect type, with patients affected by a homozygous AT type II heparin-binding site defect bearing the highest risk.[1] Given their high VTE risk, we now consider conducting primary prophylaxis with a low-dose DOAC (eg, rivaroxaban 10 mg once daily or apixaban 2.5 mg twice daily) for individuals exhibiting AT deficiency with a positive VTE family history, yet without any personal VTE events in the past. This preventive approach is, nonetheless, not supported by published evidence. The latest American College of Chest Physicians guidelines do not provide any recommendations concerning the antithrombotic management of these patients. When we consider the increasing number of individuals that are diagnosed with severe thrombophilia following systematic family screening and risk-benefit ratio of DOACs given at a low dose in secondary VTE prevention, it must be emphasized that there is clearly an unmet need for further research on extended primary thromboprophylaxis with low-dose DOACs in this setting.

Given that DOACs are already safely and efficiently used in several indications of primary and secondary venous or arterial thrombosis prevention, we suggest that it may be justified to consider and evaluate their long-term prophylactic use at low doses in patients with severe inherited thrombophilia that are at a high risk of thrombosis. Indeed, DOACs constitute the treatment of choice for stroke prevention in patients with nonvalvular atrial fibrillation, for which they have been proven to be as effective as and even safer than VKA.[3] Notably, most AF patients undergoing DOAC therapy have, in fact, never experienced any arterial thrombotic events; thus, they are given this therapy for primary prevention.

Low-dose aspirin has been approved for primary arterial thrombosis prevention in carefully selected patients and for secondary prevention in most patients with past arterial thrombotic events. Interestingly, in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, very-low-dose DOAC (rivaroxaban 2.5 mg twice daily) associated with low-dose aspirin was found to significantly reduce the risk of major cardiovascular adverse events and limb ischemia in patients suffering from peripheral artery disease.[4] The risk of major bleeding was found to be enhanced with this dual therapy, whereas no significant increase in fatal or critical organ bleeding was noted.

Notably, following major orthopedic surgery like total hip or knee replacement, DOACs are increasingly prescribed at low doses for the primary prevention of surgery-related thrombosis.[5] In the latest American Society of Clinical Oncology guidelines on thromboprophylaxis in patients with cancer, primary prevention of VTE with apixaban, rivaroxaban, or low-molecular-weight heparin is now recommended for high-risk ambulatory patients with cancer.[6] In light of recent findings, an increasing number of patients with a past VTE history may now benefit from long-term secondary prevention with low-dose DOACs, particularly rivaroxaban and apixaban. When used at low doses, these latter drugs have demonstrated antithrombotic efficacy, along with a low major bleeding risk.[7] In the AMPLIFY-EXT (Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein Thrombosis or Pulmonary Embolism) trial, major bleeding occurred in 0.2% of patients receiving apixaban at 2.5 mg twice daily for extended secondary VTE prevention (12 months after 6-12 months of VTE treatment) versus 0.5% of patients in the placebo group. In the Einstein Choice (Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic

TABLE 1 Risk of arterial or venous thrombosis according to the underlying condition

Risk factor	Risk of ischemic stroke or venous thromboembolic event
Atrial fibrillation	Ischemic stroke: RR, 2.33 (95% CI, 1.84-2.94) [12]
Previous VTE	Recurrence: OR, 15.6 (95% CI, 6.77-35.89) [13]
Heterozygous factor V Leiden	First VTE: OR, 4.22 (95% CI, 3.35-5.32) [14]
Antithrombin deficiency (types I + II)	First VTE: OR, 14.0 (95% CI, 5.5-29.0) [15] Annual absolute risk of VTE, 1.2% (95% CI, 0.8%-1.7%) [15]

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

Venous Thromboembolism) study, 0.4% of patients receiving rivaroxaban at 10 mg once daily for 12 months suffered from major bleeding versus 0.3% in the aspirin group.[7,8,9] It should be noted that the risk of major bleeding and clinically relevant nonmajor bleeding rises when DOACs are given at a full dose for extended secondary prevention.[7,10]

Finally, data on DOAC use following VTE in patients with severe inherited thrombophilia have meanwhile been reported. In a meta-analysis and systematic review by Elsebaie et al,[11] DOACs were found to be as effective as VKA in patients with thrombophilia (VTE recurrence risk: relative risk [RR], 0.70 [95% confidence interval (CI), 0.34-1.44]; all inherited thrombophilia, antiphospholipid syndrome (APS), and hyperhomocysteinemia grouped together). No significant difference was observed between the DOACs and VKA concerning the incidence of major and nonmajor bleedings in these patients (risk of major bleeding: RR, 0.84 [95% CI, 0.32-2.19]; risk of clinically relevant bleeding: RR, 0.92 [95% CI, 0.62-1.36]). However, this meta-analysis exhibited several limitations, including a low number of thrombotic events in the analyzed subgroups, as well as potential selection bias for low-risk patients in the APS subgroup, therefore rendering it impossible to precisely determine DOACs' efficacy and safety in either triple-positive APS or APS with a history of arterial thrombi.

Recently, data from the first-ever prospective cohort study focused on DOACs versus heparin and VKA for VTE treatment and secondary prevention in patients with inherited thrombophilia was published by Campello et al.[16] In this study including a large cohort of patients with thrombophilia experiencing VTE (n = 597), the DOAC efficacy in preventing VTE recurrence was comparable to that observed with VKA and heparin (cumulative incidence of recurrence during anticoagulation, 1.09% [95% CI, 0.22%-3.31%] in DOAC-treated patients versus 1.83% [95% CI, 0.74%–4.3%] in controls). For all recurrent events in the DOAC group (n = 3), precipitating factors could be demonstrated, including insufficient compliance, polycythemia vera, and APS occurrence. Notably, DOACs were revealed to be effective in a subgroup of patients with severe thrombophilia (cumulative incidence of recurrence, 2.2% [95% CI, 0.13%-8.14%] in DOAC-treated patients versus 1.77% [95% CI, 0.09%-6.62%] in controls).

Interestingly, the incidence of recurrent VTE events following anticoagulation discontinuation was significantly lower in the DOAC group versus the VKA/heparin group (9.85% [95% CI, 5.73%-16.24%] versus 21.2% [95% CI, 16.26%-27.14%] in controls). The bleeding risk was significantly higher in DOAC group (cumulative incidence, 10.2% [95% CI, 7.09%–14.36%] versus 4.97% [95% CI, 3.02%-7.97%] in controls). Nonetheless, major bleeding (n = 3) occurred only in the control group. DOACs were associated with a higher risk of clinically relevant nonmajor bleeding, especially menometrorrhagia. These study's limitations included the small sample size of patients with severe thrombophilia, in spite of all severe inherited thrombophilia types being included in the analysis. These findings, which are highly relevant for clinicians, appear to confirm DOACs' efficacy and safety in patients afflicted with inherited thrombophilia.

In conclusion, primary VTE prophylaxis using a DOAC should be considered in patients with AT deficiency or other severe inherited thrombophilia forms who carry a high risk of thrombosis. Family history, underlying genetic variants, presence of comorbidities, and risk factors for bleeding should be carefully taken into account. Recent data of a prospective cohort study are suggestive of DOACs' antithrombotic efficacy and safety in patients with severe thrombophilia and VTE. Further studies, whether randomized prospective trials or retrospective studies, are urgently needed to confirm these encouraging results in patients with AT deficiency and other severe inherited thrombophilia disorders.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors wrote and approved the final version of the manuscript.

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