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EDITORIAL COMMENT

# Efficacy of Dabigatran in Pulmonary Embolism Due to Thrombophilia in Chronic Thromboembolic Pulmonary Hypertension*

Saverio Muscoli, MD, PhD

Thrombophilia is a condition in which there is an imbalance in naturally occurring blood-clotting proteins, or clotting factors that increases the risk of thrombosis. Such disease can be identified in almost 50% of people who have an episode of thrombosis that was not linked to other causes. Thrombophilia may be primary or secondary due to other disease condition. The presence of thrombophilia does not always necessitate pharmacological treatment for prevention, although an increased risk for complications such as venous thromboembolism (VTE) has been observed in such patients (1).

Most common causes of thrombophilia are the Factor V Leiden mutation and prothrombin mutation. Other uncommon inherited forms include antithrombin deficiency, deficiencies of proteins C and S. Plasminogen activator inhibitor (PAI)-1 mutation is another very rare cause of thrombophilia. PAI-1 is a member of a family of proteins that inhibit plasminogen activators, which converts the inactive protein plasminogen into plasmin. Plasmin plays a critical role in fibrinolysis degrading fibrin and also provides localized protease activity in a number of physiological functions. PAI-1 limits the production of plasmin and mediates fibrinolysis. Increased PAI-1 levels are associated with an increased risk of thrombosis. Primary thrombophilia can present with many clinical manifestations, but VTE is the most common. The treatment of choice in such patients is oral anticoagulant therapy, even if there is not clear guidance supporting this traditional therapy for treatment or prevention of VTE in patients affected by thrombophilia.

For the acute treatment of VTE, the 2016 guidelines on Antithrombotic Therapy for VTE disease from the American College of Chest Physicians recommend therapy with direct oral anticoagulants (DOACs) if there are no contraindications (2). For patients affected by hereditary thrombophilia, the European Society of Cardiology 2019 guidelines for the diagnosis and management of acute pulmonary embolism suggest an indefinite anticoagulant treatment after a first episode of PE occurring in the absence of a major reversible risk factor (3).

There are few data about the use of dabigatran in patients affected by thrombophilia with VTE. The RE-COVER/RE-COVER II (Prevalence of Post-Thrombotic Syndrome in Deep-Vein Thrombosis Patients Treated With Dabigatran) and REMEDY (Secondary Prevention of Venous Thrombo-Embolism) trials showed dabigatran efficacy and safety also in patients affected by thrombophilia (4).

Chronic thromboembolic pulmonary hypertension (CTEPH) is a particular subtype of pulmonary hypertension (PH) characterized by the persistent obstruction of pulmonary arteries by organized thrombi, with concomitant microvascular arteriopathy, resulting in progressive PH. CTEPH is often underdiagnosed and has an incidence between 0.1% and 9.1% in the first 2 years after a symptomatic PE event. Medical treatment

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From the Department of Cardiology, Fondazione Policlinico "Tor Vergata," Rome, Italy. Dr. Muscoli has reported that he has no relationships relevant to the contents of this paper to disclose.

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consists of lifelong oral anticoagulation with vitamin K antagonists, also after successful pulmonary endarterectomy (PEA). No data exist on the efficacy and safety of DOACs in patients affected by CTEPH (5).

In this issue of *JACC: Case Reports,* in their case report on chronic thromboembolic pulmonary hypertension due to thrombophilia and incidentally diagnosed atrial septal defect, Kilinc et al. (6) described how to manage a complex case of a patient hospitalized for pulmonary embolism, affected by thrombophilia, who developed atrial fibrillation and CTEPH with accidental diagnosis of ostium secundum atrial septal defect (ASD).

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It is noteworthy that the authors have interfaced the problem with a multidisciplinary team, reaching a diagnosis and subsequently a good therapeutic treatment. In this difficult and complex diagnostic process, the authors have performed all tests for differential diagnoses. These examinations are very important to carry out a correct therapeutic procedure. However, it should be highlighted that pulmonary function tests and diffusing capacity of the lungs for carbon monoxide were normal, and the patient walked 500 m without desaturation on a 6-min hall walk. This explains the unpredictability of the disease and the difficulty in carrying out the diagnosis. To perform the correct diagnosis, a ventilation/perfusion (V/Q) scan was crucial and was very suspicious for CTEPH. The V/Q scan is the preferred and recommended screening test for chronic thromboembolic disease in patients with PH. Using computed tomography pulmonary angiogram for screening may lead to potential misdiagnosis of pulmonary artery hypertension (PAH) and underdiagnosis of CTEPH, especially in patients with distal disease (7).

V/Q scan has a sensitivity of >96%, and a normal result can rule out CTEPH. An abnormal V/Q scan is suggestive of CTEPH—even when a computed tomography scan is negative. Despite consistent recommendations that V/Q scanning be used to screen for CTEPH, its underutilization in screening PH increases misdiagnosis of PAH. Furthermore, according to the guidelines, right- and left-heart catheterization were performed. Also, pulmonary angiography was performed, although at this point, perhaps, it was a fairly superfluous examination as the diagnosis had already been made using the V/Q scan and computed tomography pulmonary angiogram. Pulmonary angiography is an invasive test that is not free of risk, and it can misdiagnosis of small thrombi <2 mm. Another issue in this case was how to manage the secundum ASD. Nowadays, when possible, ASD treatment is percutaneous. In this case, the patient had to undergo surgery; the decision of a surgical approach using the patch was correct.

A very intuitive choice was to also perform a genetic test. This in fact, evidenced a mutation for the PAI-1 (5G>4G) gene. This mutation, as described in the previous text, is responsible for a rare form of thrombophilia that resulted in pulmonary embolism.

The patient was treated successfully with a PEA, and then, the authors decided to move from vitamin K antagonist to a DOC, in this case, to dabigatran.

There are no data on DOACs after PEA to prevent further embolization, but in this case, the patient had an uneventful 2 year-follow-up on dabigatran.

Therefore, although much remains to discover and clarify, the widespread use of DOACs in AF, PE, and VTE is very promising in expanding their regular use in CTEPH, also after PEA.

Another strength of this case report is that, in a similar case, the appropriate use of a genetic test allowed for diagnosis and therapeutic treatments that are otherwise not feasible. Further work is needed to understand when to routinely use genetic testing.

**ADDRESS FOR CORRESPONDENCE:** Dr. Saverio Muscoli, Department of Cardiology, Fondazione Policlinico "Tor Vergata," Viale Oxford 81, 00133 Rome, Italy. E-mail: saveriomuscoli@gmail.com.

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**KEY WORDS** atrial fibrillation, pulmonary hypertension, thrombosis