Tark Abou-Elmagd, MD, MSc, MBBCh
Department of Internal Medicine, Cape Fear Valley Medical Center, Fayetteville, NC

Shraddha Narechania, MD
Fellowship Program Director, Pulmonary Medicine, Campbell University School of Osteopathic Medicine, Cape Fear Valley Medical Center, Fayetteville, NC; Assistant Professor, Campbell University Jerry M. Wallace School of Osteopathic Medicine, Lillington, NC

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should I start anticoagulation in my patient newly diagnosed with pulmonary hypertension?

A: The decision about starting anticoagulation along with targeted therapy in patients with pulmonary hypertension hinges on the subtype of pulmonary hypertension the patient has. A review of the latest guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)—and the evidence to date—can help guide decision-making.[1] But first, let's look at why we consider anticoagulation for pulmonary hypertension in the first place.

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WHY CONSIDER THERAPEUTIC ANTICOAGULATION IN PULMONARY ARTERIAL HYPERTENSION?

Pulmonary hypertension is defined as a mean arterial pulmonary pressure of 20 mm Hg or higher measured during right heart catheterization, and patients diagnosed with the disease are grouped according to the underlying cause of the elevated pulmonary artery pressure (**Table 1**).[1] Before targeted medical therapy for pulmonary hypertension was developed, anticoagulation therapy (mainly vitamin K antagonists) was prescribed in about 90% of patients with World Health Organization (WHO) group I pulmonary hypertension, ie, pulmonary arterial hypertension.[2,3] This practice was driven by evidence showing hypercoagulability in patients with pulmonary arterial hypertension, including an increased prevalence of thrombotic lesions, activation of the coagulation system, and resistance to fibrinolysis.[3] With the development of targeted medical therapies, the frequency of therapeutic anticoagulation in these patients has dropped from 90% to 50%, according to data from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA),[2] Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL),[4] and other trials.[3]

Evidence shows that the procoagulant and fibrinolytic activity of the pulmonary arterial endothelium is altered in pulmonary arterial hypertension. This is reflected by increased plasma levels of von Willebrand factor and plasminogen activator inhibitor type 1 observed in patients with this form of pulmonary hypertension.[5] Notably, plasminogen factor inhibitor is found in higher concentrations in arterial samples compared with mixed venous samples, suggesting intrapulmonary production. Further, in response to the vascular abnormalities in pulmonary hypertension, platelets release mediators with procoagulant, mitogenic, and vasoconstrictor effects that contribute to the prothrombotic state, including thrombin, thromboxane A2, platelet-activating factor, serotonin, platelet-derived growth factor, transforming growth factor beta, and vascular endothelial growth factor.[5,6] It is unclear whether thrombosis and platelet dysfunction are causes—or consequences—of pulmonary arterial hypertension.

Pulmonary hypertension is a progressive condition that can lead to right-sided heart failure. The presence of right ventricular dysfunction has been identified as a potential risk factor for venous thromboembolism, although the evidence supporting this association is not strong.[7] Left-sided heart failure, however, is considered an independent risk factor for venous thromboembolism.[2] Furthermore, patients with pulmonary

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TABLE 1
World Health Organization (WHO) classification of pulmonary hypertension

WHO classification	Etiology
Group I: pulmonary arterial hypertension	Idiopathic; drug- or toxin-related; associated with connective tissue disease, human immunodeficiency virus infection, portal hypertension, congenital heart disease, schistosomiasis; persistent pulmonary hypertension of the newborn; pulmonary arterial hypertension with venous or capillary involvement
Group II: pulmonary hypertension associated with left heart disease	Heart failure, valvular heart disease, congenital or acquired heart conditions leading to postcapillary pulmonary hypertension
Group III: pulmonary hypertension associated with lung disease, hypoxia, or both	Obstructive lung disease or emphysema, restrictive lung disease, lung disease with mixed pattern, hypoventilation syndromes, hypoxia without lung disease, developmental lung disease
Group IV: pulmonary hypertension associated with pulmonary artery obstruction	Chronic thromboembolic pulmonary hypertension, other pulmonary artery obstructions (malignant tumors, sarcomas)
Group V: pulmonary hypertension with unclear or multifactorial mechanisms	Hematologic disorders, systemic disorders, metabolic disorders, chronic renal failure with or without dialysis, fibrosing mediastinitis, pulmonary tumor thrombotic microangiopathy

Based on information from reference 1.

hypertension can have significant dyspnea on exertion, resulting in immobility, which is a risk factor for venous thromboembolism.[5–7]

IN WHICH PULMONARY HYPERTENSION GROUPS SHOULD ANTICOAGULATION BE CONSIDERED?

According to the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension,[1] the decision about starting anticoagulation in patients with pulmonary arterial hypertension (WHO group I pulmonary hypertension) should be individualized, while lifelong anticoagulation is recommended in patients with chronic thromboembolic pulmonary hypertension (WHO group IV).

Pulmonary arterial hypertension (WHO group I)

Current evidence regarding anticoagulation therapy in patients with pulmonary arterial hypertension remains insufficient, with conflicting results from major registry studies such as COMPERA[2] and REVEAL[4] and the most recent meta-analyses done by Khan et al[6] and Wang et al[8] (**Table 2**).[2,4,6,8–12] COMPERA[2] compared patients with idiopathic pulmonary arterial hypertension who received anticoagulation therapy (predominantly vitamin K antagonists) with those who did not receive it, and found a significant survival benefit for those receiving anticoagulants. These findings are consistent with the results of the meta-analysis conducted by Khan et al.[6] REVEAL,[4] however, showed no significant survival benefit for patients with group 1 pulmonary hypertension who received anticoagulation therapy compared with those who did not receive it. This lack of benefit may be explained by REVEAL's inclusion of patients with more severe disease, characterized by lower functional status, multiple comorbidities, and need for multiple therapies at time of enrollment. These findings were consistent with the Wang et al[8] meta-analysis.

Anticoagulation therapy is generally not recommended in pulmonary arterial hypertension associated with human immunodeficiency virus (HIV) or systemic sclerosis due to the higher risk of bleeding (systemic sclerosis and HIV) and potential drug interactions (HIV).[1] Vitamin K antagonists are recommended for pulmonary arterial hypertension associated with connective tissue diseases *if* the patient is predisposed to thrombophilia (eg, antiphospholipid syndrome). In patients with pulmonary arterial hypertension due to congenital heart disease, anticoagulation may be considered in the presence of a large pulmonary artery aneurysm with thrombus, history of thromboembolic events, or both.[1]

Chronic thromboembolic pulmonary hypertension (WHO group IV)

Non–vitamin K antagonist oral anticoagulants are recommended in the first 3 months after acute pulmonary embolism is diagnosed.[13] Diagnostic reevaluation for chronic thromboembolic pulmonary disease

TABLE 2
Meta-analyses and original studies evaluating anticoagulation therapy in PAH

Study, design, population	Outcomes	Results	Comments and limitations
Rich et al (1992)[9] Prospective post hoc cohort analysis of 64 patients with PAH	5-year survival	Improved survival in the 35 patients who received VKA	VKA started if lung perfusion scan was abnormal
Ngian et al (2012)[10] Prospective multicenter cohort of 117 patients with incident CTD-PAH	3-year survival	Improved survival in patients with CTD-PAH who received VKA	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation
Johnson et al (2012)[11] Retrospective cohort study of 66 patients with idiopathic PAH and 98 patients with SSc-PAH	3-year survival Time from PAH diagnosis until death from all causes Probability that VKA improved median survival by ≥ 6 months	VKA showed low probability for improving survivability in idiopathic PAH and SSc-PAH	Small study size Included all patients exposed to VKA regardless of minimum duration or dosing Didn't include all prognostic factors for survival of patients with PAH
COMPERA (2014)[2] Prospective post hoc cohort analysis of 1,283 patients with PAH (800 idiopathic, 208 SSc-PAH)	3-year survival	Improved survival in patients with idiopathic PAH who mainly received VKA, but not in other forms of PAH	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation
REVEAL (2015)[4] Prospective post hoc cohort analysis of 144 patients with idiopathic PAH and 43 with SSc-PAH who received VKA anytime during study, matched with 187 who did not	3-year survival	Similar survival between 2 groups Lower survival in patients with SSc-PAH who had taken VKA	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation Mix of prevalent and incident cases
HEMA-HTP (ongoing)[12] Prospective multicenter cohort of 203 patients (88 PAH, 115 chronic thromboembolic pulmonary hypertension); 152 on VKA, 51 on direct oral anticoagulants, 4 on combined antiplatelet therapy	Major bleeding (International Society on Thrombosis and Haemostasis definition)	Preliminary results showed significant bleeding risk, with 22 patients experiencing major bleeding (12 with PAH, 10 with chronic thromboembolic pulmonary hypertension) Two patients died from major bleeding	
Khan et al (2018)[6] Systematic review and meta-analysis of 12 studies (8 retrospective, 4 prospective); 2,512 patients (1,342 on anticoagulation; 1,170 controls)	Impact of adjunctive oral anticoagulants in PAH and whether response differed by PAH subtype	Anticoagulation significantly reduced mortality in overall PAH group—reduction most significant in idiopathic PAH, with no difference in CTD-PAH Increased mortality seen in patients with SSc-PAH on anticoagulation therapy	Absence of randomized clinical trials Heterogeneity of results, possibly secondary to various concomitant therapies Possibility of publication bias
Wang et al (2020)[8] Systematic review and meta-analysis of 8 observational studies (1,812 patients with idiopathic PAH)	Efficacy of anticoagulation therapy in idiopathic PAH	No significant difference in survivability in treated vs untreated patients with idiopathic PAH	Absence of randomized clinical trials Definitions and patient inclusion criteria differed between the 8 studies, leading to bias Unbalanced patient characteristics

COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD = connective tissue disease; HEMA-HTP = Bleeding Frequency Under Anticoagulant Treatment in Pulmonary Hypertension; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; SSc = systemic sclerosis; VKA = vitamin K antagonist

or chronic thromboembolic pulmonary hypertension is recommended (class 1 recommendation) for patients who, after this time period, have new-onset dyspnea or exercise limitations. The guidelines say this evaluation should include a ventilation-perfusion scan or computed tomography pulmonary angiography to assess for persistent perfusion defects, along with evaluation for pulmonary hypertension using echocardiography.[13]

If, after 3 months, pulmonary hypertension is evident or persists, therapeutic anticoagulation with a vitamin K antagonist is needed indefinitely.[13] Although non–vitamin K antagonist oral anticoagulants have been used, this practice is not backed by robust evidence from randomized clinical trials, and these agents have been shown to have a higher incidence of recurrent thromboembolic events.[1]

Patients with chronic thromboembolic pulmonary disease should be screened for antiphospholipid syndrome, as the syndrome is present in 10% of them.[1] Once antiphospholipid syndrome is diagnosed, lifelong vitamin K antagonist use is indicated, regardless of pulmonary hypertension status.

ANTICOAGULANT CHOICE, INTERNATIONAL NORMALIZED RATIO GOALS, AND BLEEDING RISK

Currently, the choice of therapeutic anticoagulants is limited to vitamin K antagonists because these agents have fewer interactions with targeted therapy for pulmonary arterial hypertension. There are no randomized clinical trials comparing the efficacy of vitamin K antagonists vs non–vitamin K antagonist oral anticoagulants in patients with pulmonary arterial hypertension.[3,4]

The goal international normalized ratio in WHO group IV pulmonary hypertension has not been well defined, and the current goal of 2.0 to 3.0 has been extrapolated from venous thromboembolism studies.[3] The 2022 ESC/ERS guidelines[1] do not identify an international normalized ratio goal, while some studies recommended a goal of 1.5 to 2.0.[3]

Before starting anticoagulation therapy for pulmonary arterial hypertension or thromboembolic pulmonary hypertension, the risk of bleeding should be discussed with the patient. We do not have data from a completed prospective randomized controlled trial on the risk of major bleeding with anticoagulation therapy in either of these pulmonary hypertension subtypes. However, an ongoing trial (Bleeding Frequency Under Anticoagulant Treatment in Pulmonary Hypertension[12]) is looking at the risk of major bleeding in these patient populations.Preliminary results showed a high risk of major bleeding, including fatal bleeding, but we will have to wait for the full results to identify the specific risk factors for the bleeding.

THE BOTTOM LINE

With the dramatic evolution of modalities for the management of pulmonary hypertension over the past 2 decades, a main dilemma is the adjuvant use of anticoagulation to prolong survival. The 2022 ESC/ERS guidelines[1] suggest that the decision to start anticoagulation in patients with pulmonary arterial hypertension should be individualized, and we agree with this recommendation, while anticoagulation is recommended in all patients with chronic thromboembolic pulmonary hypertension. Vitamin K antagonists are the preferred agents. Anticoagulation is not recommended in patients with pulmonary arterial hypertension due to systemic sclerosis or HIV due to high risk of bleeding in both conditions and drug interactions in HIV.

Comparative studies are needed to explore the risks and benefits of vitamin K antagonists vs non–vitamin K antagonist oral anticoagulants, given that the latter are often preferred because of their ease of use. Moreover, robust prospective randomized clinical trials are needed to assess whether anticoagulant therapy provides a survival benefit in patients diagnosed with pulmonary arterial hypertension.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: *Tark Abou-Elmagd, MD, MSc, MBBCh, Department of Internal Medicine, Cape Fear Valley Medical Center, 1638 Owen Drive, Fayetteville, NC 28304; colorado_94@outlook.com*