The Complicated Question of Anticoagulation in Pulmonary Arterial Hypertension: Time to Get Some Simple Answers

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According to Dr Seuss, “Sometimes the questions are complicated and the answers are simple.”1 However, when practitioners are asked if anticoagulation is beneficial in pulmonary arterial hypertension (PAH), it is the question that is simple and the answer that is quite complicated.

The histology of PAH is characterized by plexiform lesions, vasoconstriction, medial hypertrophy, intimal hyperplasia, perivascular inflammation, and thrombotic lesions within the pulmonary vasculature.2-4 The aetiology of these pathologic lesions remains unclear but has been associated with drug exposures, genetic mutations, and other systemic diseases including cirrhosis, HIV, and collagen vascular diseases. Despite the diverse risk factors for the development of PAH, the therapeutic options currently available have focused on pulmonary vasodilation and improvement in right ventricular function.5,6 Randomized controlled trials (RCTs) of anti-inflammatory and antiangiogenic agents have failed to show clinical benefit or decrease the vascular remodelling seen in PAH.7,8 Although pulmonary vasodilators have contributed to an improved prognosis in PAH,9 1-year mortality rates remain considerable at 7%-17%.10,11 Additionally, mortality differs between phenotypes of PAH, and most particularly is worse in scleroderma-associated PAH.12 In this setting, efforts to define optimum pharmacotherapy in PAH and individualize therapy based on clinical phenotype are important tasks facing PAH providers.

One potential therapeutic approach that has remained somewhat controversial is the use of warfarin and anticoagulation in PAH. In 1992, Rich and colleagues found a potential therapeutic role for systemic anticoagulation in PAH. However, perhaps more importantly, this study identified a potential therapeutic role for systemic anticoagulation in PAH worthy of further study. More recently in 2013, data from the Compera, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) similarly found a significant survival benefit with the use of warfarin in patients with idiopathic PAH (iPAH).14 However, in the 2 decades between these publications, there remains no RCT to truly define the role of warfarin in PAH.

Despite the lack of RCTs, numerous associations have recommended the use of systemic anticoagulation in PAH. The 2009 American College of Cardiology Foundation/American Heart Association expert consensus document on pulmonary hypertension recommended warfarin anticoagulation in patients with iPAH for a target international normalized ratio of 1.5-2.5. Acknowledging the dearth of information in associated forms of PAH, including scleroderma-associated PAH, the same consensus document recommended anticoagulation for patients with more advanced disease who do not have an obvious contraindication. The guidelines from European societies (European Society of Cardiology/European Respiratory Society) offer a class IIA recommendation for the use of oral anticoagulation for patients with iPAH, anorexigen-induced PAH, and heritable PAH.16 Recent published documents from the Fifth World Symposium on Pulmonary Hypertension continue to give a class IIA or IIB recommendation for anticoagulation in patients depending on the type of Group I PAH.5

In the article by Caldeira and colleagues17 in this issue of the Canadian Journal of Cardiology, the authors performed a systematic review of the PAH literature to assess the evidence for anticoagulation use in this disease. From the 9 cohort studies that the authors identified, of which only 2 were prospective, the authors found a 31% decrease in mortality among PAH patients treated with warfarin. The work of Caldeira and colleagues is important because of the robust nature of their analysis, which reinforces the potential role for anticoagulation in PAH. However, perhaps more importantly, this study demonstrates the paucity of randomized data for this important clinical question.
As the authors note, “performing meta-analysis using observational data raises methodological and interpretational concerns.” None of the trials or registries included were designed with the primary purpose of studying the effects of warfarin on survival in PAH. Of the 9 studies in this meta-analysis, 5 were performed in an era in which there were no Food and Drug Administration-approved pulmonary vasodilators available (excluding calcium channel blockers). Only 3 studies performed outcome adjustments for parameters that are known to affect prognosis in PAH (right ventricular failure, syncope, and functional class, among others). The article by Caldeira and colleagues also highlights the variability in characteristics of the patient populations: 6 studies had a mean age of younger than 45 years and in the 3 other studies the populations had a mean age older than 60 years. This might also reflect a changing demographic within PAH because the latter 3 studies were all published since 2011. However, these differences in baseline characteristics emphasize the difficulties associated with comparing clinical trials and registries. This article also demonstrates that there is very little objective information available on the role of anticoagulation in connective tissue disease-associated PAH, with only 1 trial enrolling significant numbers of such patients.

The disparate evidence for the role of warfarin in PAH has translated into varying clinical practice. For example, in some RCTs, warfarin is used in 36% of patients, and in other study populations the use of warfarin is close to 100%. It is difficult to identify pharmaceutical interactions between PAH therapies and anticoagulation when there is variability in prescribing patterns of warfarin in clinical trials. The Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) trial was unique in that it did identify an increased incidence of subdural hematoma in PAH patients treated with oral anticoagulants and imatinib, although the mechanism for this is unclear. Another problem with anticoagulation is that rates of bleeding probably differ between different forms of associated PAH. Correspondingly, the increased bleeding complications seen in the associated forms of PAH might contribute to the lack of benefit from anticoagulation in these populations. In the COMPERA study, increased gastrointestinal complications including gastric hemorrhage were seen in scleroderma patients when they were treated with anticoagulants. Therefore, any practical recommendations regarding anticoagulation in PAH must take into account the form of PAH and the associated comorbidities.

A recent randomized study on the role of warfarin in sickle cell disease-associated PAH was unfortunately discontinued because of low enrollment. This study again highlights the difficulties in arriving at firm recommendations in this disease process. However, with the arrival of novel anticoagulants into the clinical arena, many of which have shown efficacy in thromboembolic pulmonary vascular disease, we are presented with a unique opportunity to study anew the role of anticoagulation in PAH. With new clinical trials in PAH being designed to target metabolism, inflammation, and vasodilation, it is time to reinvigorate our efforts at investigating the value of inhibiting thrombotic pathways. Whether such an approach will improve outcomes in PAH remains to be seen. However, at the very least we need to learn the lessons emanating from the warfarin studies, as presented here by Caldeira and colleagues, and design prospective, adequately-powered randomized trials of novel anticoagulants, considering in their design the many forms of PAH, so that we provide some simple answers to the complicated question of anticoagulation in PAH.

**Disclosures**

The authors have no conflicts of interest to disclose.

**References**


