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| **INVITED REVIEW**

Anticoagulant treatment in patients with pulmonary arterial hypertension associated with systemic sclerosis: More shadows than lights

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ABSTRACT

Pulmonary arterial hypertension is a chronic and progressive disease characterized by elevated pulmonary artery pressure and pulmonary vascular resistance leading to heart failure and premature death. Pulmonary arterial hypertension is characterized by proliferative and obstructive lesions in the distal pulmonary arteries and some descriptions include also thrombotic lesions. Despite this, in an era when multiple effective pulmonary arterial hypertension therapies are available, the role of anticoagulation in the treatment of pulmonary arterial hypertension remains uncertain. In particular, anticoagulant treatment in pulmonary arterial hypertension associated with connective tissue disease seems to be associated with unfavorable risk to benefit ratio due to an increased rate of bleeding from the gastrointestinal tract. However, anticoagulation may be required in conditions with increased thrombophilia like in the presence of lupus anticoagulant phenomenon or in the presence of anticardiolipin antibodies.

Keywords: Anticoagulation, Pulmonary arterial hypertension, Systemic sclerosis, Therapy

Pulmonary arterial hypertension (PAH) is a severe and chronic disease characterized by a progressive obstructive remodeling of the distal pulmonary arteries that results in increased pulmonary vascular resistance and pulmonary arterial pressure. PAH includes a heterogeneous group of clinical entities such as idiopathic PAH (IPAH), heritable PAH (HPAH), drug- and toxin-induced PAH, and PAH associated with congenital heart disease, connective tissue disease (CTD), and HIV infection (1).

The exact processes that initiate the pathological changes seen in PAH are largely unknown. It is hypothesized that the interaction between constitutional predisposition and environmental risk factors may be involved in the initial stages of the disease. However, the exact role of the autoantibodies in CTD or the viral involvement in HIV infection on the pathogenesis of associated PAH is unclear. It appears that a specific injury on the vessel wall of distal pulmonary arteries may initiate, in predisposed individuals, a pathobiological cascade of events leading to a common final pathological obstructive condition. Pathological lesions in PAH patients affect the distal pulmonary arteries (<500 μm of diameter) and are characterized by medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening with moderate perivascular inflammatory infiltrates, complex lesions (plexiform and dilated), and also thrombotic lesions (2).

It is unclear whether thrombotic vascular lesions are an integral part of the pulmonary vascular pathology or are simply an epiphenomenon. In early pathological series, a high prevalence of vascular thrombotic lesions at postmortem examination were described in patients diagnosed as IPAH (3). However, it is uncertain whether the differential diagnosis with chronic thromboembolic pulmonary hypertension (CTEPH) was performed according to the modern criteria (1). There is some biological rationale to support the hypothesis that thrombotic processes are a significant pathophysiologic feature of PAH and that its evolution contributes to disease

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Table I - Recent studies of anticoagulation therapy in PAH

Author		Subjects	Exposure	Outcome
Olsson et al. (14)	COMPERA registry	*1283*	Vitamin K antagonists, heparins, and novel oral anticoagulation	
		IPAH (n=800)		Better 3-year survival (p=0.006) in patients on anticoagulation compared with patients who never received anticoagulation
		SSc-PAH (n=208)		Trend (p=0.08) towards a worse outcome associated with anticoagulation
Preston et al. (20)	REVEAL registry (matched study)	*374*	Vitamin K antagonist	
		IPAH (n=288)		No survival difference with warfarin in IPAH patients in comparison with matched controls.
		SSc-PAH (n=86)		No survival difference with warfarin in SSc-PAH patients in comparison with matched controls.
Galie et al. (21)	SERAPHIN trial	*742* (379 on anticoagulation therapy and 363 no)	Vitamin K antagonist	No significant difference in the risk of morbidity and mortality observed in patients not on anticoagulant therapy compared with those on anticoagulant therapy between IPAH and non-IPAH patients

IPAH=idiopathic pulmonary arterial hypertension; SSc=systemic sclerosis.

progression (4). However, these abnormalities apparently have not been described in the associated forms of PAH, including CTD-PAH.

PAH is a common complication of systemic sclerosis (SSc), relatively uncommon in mixed CTD and systemic lupus erythematosus and rare in rheumatoid arthritis, Sjogren's syndrome, and inflammatory myositis (5). Patients with CTD-PAH, especially with PAH-SSc, have been included in many of the randomized controlled trials with drugs in PAH, and usually, they represent the second largest group after IPAH. Several studies demonstrate that CTD-PAH patients have a worse prognosis as compared with other PAH subgroups and that patients with SSc-PAH have particularly poor outcomes (6). Nevertheless, the advanced PAH therapies determine improvements in clinical, haemodynamic, and exercise capacity measures as well as health-related quality-of-life outcomes, also in SSc-PAH patients compared with placebo (7, 8).

Oral anticoagulant treatment has been indicated for patients with IPAH, HPAH, and PAH due to anorexigens in different editions of the pulmonary hypertension (PH) guidelines with variable degrees of recommendation. Supporting evidence and safety data, however, are limited. In fact, only eight observational studies (two prospective and six retrospective) have evaluated the effect of chronic anticoagulation on the outcome of patients with IPAH, and six of them reported apparently favorable outcomes (3, 9-15). In 2006, a qualitative systematic review on anticoagulation in PAH performed by Johnson concluded that the literature appears to support a treatment effect of anticoagulation therapy with warfarin on mortality in IPAH but requiring randomized clinical trials (16). In fact, none of the studies was blinded, randomized, and placebo-controlled. Second, the studies date to a time when there was no specific therapy for PAH (only empiric use of vasodilators) and the size of the sample was extremely poor. Benefit of oral anticoagulation in CTD-PAH is even less clear as this strategy has been extrapolated from the questionable data collected in IPAH patients (17).

A Bayesian analysis of observational data from a longitudinal cohort of patients with SSc-PAH or IPAH concluded that there is a low probability that warfarin improves survival in SSc-PAH and IPAH. Given the availability of multiple PAH therapies with evidence-based clinical benefits, the potential additional effect of warfarin to improve outcomes is unclear if any (18).

Recently, a comparative prospective registry-based study (COMPERA) apparently showed that IPAH anticoagulated patients had a better survival as compared to non-anticoagulated ones. No survival benefit was observed in patients with PAH associated with other conditions like CTD-PAH (14). In this population, there is a trend (p = 0.08) towards a worse outcome associated with anticoagulation (14). However, the analysis performed in this study is influenced by the "immortal time bias" and even the favorable effect observed in IPAH patients is questionable (19). In fact, the survival in this study was computed since the inclusion of the patients in the registry and not since the actual starting of the anticoagulant therapy. The time between

these two time-points is defined "immortal time" because the patient cannot die before receiving the first dose of anticoagulant therapy. In the study analysis, the "immortal time" was considered as survival on anticoagulant therapy thus inappropriately providing this survival extension to the treated patients as compared with the non-anticoagulated ones (19). In the REVEAL registry analysis, this bias was avoided and no significant survival increase was observed in IPAH patients who started warfarin while in the registry. In addition, in SSc-PAH patients, long-term warfarin treatment was associated with worse survival as compared with patients not receiving warfarin even after adjusting for confounders (20). Immortal time bias was avoided also in the comparison of PAH patients with or without anticoagulant treatment enrolled in the SERAPHIN trial, and no difference in the outcome was observed in patients not on anticoagulant therapy compared with those on anticoagulant therapy between IPAH and non-IPAH patients (IPAH—hazard ratio (HR): 0.97, 0.72–1.32 vs non-IPAH—HR: 0.71, 0.49–1.02; p = 0.19) (21). Newest studies evaluating a role for anticoagulation in PAH, with mortality as an end point, are summarized in Tab. I. The detrimental effect of long-term warfarin in CTD-PAH patients may be explained by comorbidities. In fact, there is increased risk of bleeding from gastrointestinal telangiectasias or arteriovenous malformations in SSc-associated PAH patients as compared to IPAH or CTEPH patients (22, 23). In fact, in the retrospective analysis of PAH patients treated in the VU Medical Center hospital of Amsterdam, bleeding event rates with vitamin K antagonist drugs were 5.4 per 100 patient-years in patients with IPAH, 19 per 100 patient-years in CTD-PAH patients, and 2.4 per 100 patient-years in CTEPH patients (23). Major bleedings were independent of age, sex, target international normalized ratio (INR) range, documented INR actual value, vitamin K antagonist type, or right atrial pressure, but was associated with the concomitant use of prostacyclin analogues (23). In fact, the concurrent use of PAH-specific therapies with antiplatelet effect such as prostacyclin analogues may increase the risk of bleeding for the combined inhibition on multiple factors of the coagulation cascade.

A randomized controlled trial with the new oral anticoagulant apixaban in SSc-PAH patients (SPHInX registration number ACTRN12614000418673) is ongoing and may provide us with long awaited information on this treatment approach. In fact, this is the first clinical trial ever to evaluate the efficacy, safety, and cost-effectiveness of anticoagulant therapy in addition to approved PAH drugs in SSc-PAH patients (24).

In conclusion, the use of anticoagulant treatment remains controversial in patients with PAH and may be detrimental in the majority of patients with CTD-PAH. Anticoagulant treatment may be considered in conditions with PH and increased thrombophilia like in the presence of lupus anticoagulant phenomenon or in the presence of anticardiolipin antibodies.

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