Editorial

Registry to evaluate early and long-term disease management in PAH (REVEAL)

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Pulmonary artery hypertension (PAH) is a condition with significant clinical symptoms, poor quality of life and early mortality. Heath-Edwards classification which was based primarily on pulmonary vascular histology changes include a spectrum of lesions like vasoconstriction, intimal hyperplasia, medial hypertrophy, plexiform arteriopathy, perivascular inflammation, and thrombotic lesions within the pulmonary vasculature (1-3).

Abnormalities of antithrombotic factors and fibrinolytic system contributing to a prothrombotic state have been discussed in the etiopathogenesis of patients with idiopathic pulmonary arterial hypertension (IPAH) (4). Thrombotic pulmonary vascular lesions results in pulmonary vascular remodelling, luminal narrowing and increased vascular resistance leading to the progression of the disease process (5).

Although there are a wide range of pulmonary arterial vasodilators which have contributed to an improved prognosis in PAH (6), 1-year mortality rates remain considerable at 7–17% (7) and is particularly worse in scleroderma-associated PAH (8).

The use of warfarin is based on the concept that *in situ* thrombosis plays a potential role in disease progression. An analysis from the Registry to Evaluate Early and Long-Term Disease Management in PAH (REVEAL), the largest PAH registry ever developed and published in this circulation issue further reinforces the questionable role of warfarin in PAH management (9). Although this registry has used newer statistical methods to analyze the data and adjustments for the confounding factors, many unknown confounding factors might still influence the outcome of the impact of specific drug therapy on the PAH disease progression. Since there are no randomized trials so far on the role of anticoagulation in PAH and unlikely to come, registry-based analyses remain the best available source of information.

In a landmark pathologic study of the lung vessels by Wagenvoort (10) involving 156 clinically diagnosed cases of primary pulmonary hypertension, 20% had evidence of thromboembolic pulmonary hypertension and 4% had mixed vasoconstrictive and thrombotic lesion suggesting that these subsets may have better outcome when treated with warfarin than others with nonthrombotic lesions.

A study of 120 PAH patients by Fuster *et al.* (2) revealed that 18% had autopsy findings most consistent with chronic thromboembolic pulmonary hypertension and the use of systemic anticoagulation therapy was one of the strongest positive prognostic factors. One- and 3-year survival respectively was 80% and 50% for those receiving warfarin and 60% and 25% for those not receiving warfarin. The low rate of survival was likely due to the non-availability of specific pulmonary vasodilators.

A subsequent study by Rich *et al.* (11) concluded that warfarin when added to calcium channel blocker (CCB) improved survival in patients who were either CCB responders or non-responders. Non-responders who were treated with warfarin in addition to CCBs benefitted better than those who were not. Warfarin users also had a better survival than the nonusers at 1, 3 and 5 years (91%, 62%, 47% *vs.* 52%, 31%, 31%, respectively).

A retrospective cohort study of PAH patients by Kang *et al.* (12) showed survival rates at 1, 3, 5, and 10 years were 100.0%, 100.0%, 88.9%, and 74.1%, respectively, in the warfarin group, and 85.7%, 69.7%, 48.9%, and 16.3%, respectively, in the non-warfarin group and a 2-fold higher

mean survival (12.0 years in the warfarin group *vs.* 6.1 years in the non-warfarin group).

As a result of these studies, warfarin became a well accepted drug in the armamentarium of PAH therapy and widely used in all group 1 PAH patients as recommended in the guidelines.

The use of warfarin is fraught with risks like difficulty in maintaining therapeutic international normalized ratio, labile anticoagulation profile in patients with advanced right ventricular dysfunction, drug interactions and bleeding complications including fatal cerebral hemorrhage and serious gastrointestinal bleeding especially in scleroderma associated PAH with gastrointestinal telangiectasia (13).

In a meta-analysis by Johnson *et al.* (14), 5 out of 7 observational studies suggested survival benefit associated with warfarin in the treatment of IPAH, whereas two observational studies were not in favor of this association. These are epidemiological studies with inherent methodological issues, including selection bias and unmeasured confounding factors leading to dubious conclusions regarding the effect of anticoagulation therapy on survival in patients with IPAH.

The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), enrolled patients from seven European countries with a major contribution from German centers (15). Anticoagulation usage was 45% and 65% in connective tissue disease associated PAH and IPAH respectively.

Warfarin anticoagulation was associated with better outcomes in IPAH cohort in contrast to worse outcome in connective tissue associated PAH. In scleroderma-associated PAH, warfarin therapy had an increased hazard for death in COMPERA study, in concordance with REVEAL analysis who had similar adverse outcomes (unadjusted hazard ratio, 2.03, P=0.03; REVEAL risk score–adjusted hazard ratio, 1.60, P=0.15) compared with those who were not on warfarin. The role of warfarin in the management of scleroderma-associated PAH is doubtful or maybe it is harmful. In contrast to the concordant results regarding the impact of warfarin treatment in scleroderma-associated PAH in REVEAL and COMPERA registry, outcome of warfarin in IPAH cohort did not show any benefit in the REVEAL registry. Both the registries differ greatly in their patient characteristics and management patterns which would possibly explain the varying outcomes in the IPAH cohort.

The difference in the outcome of these two registries may also be very well explainable by variation in many features like mean age of patients (68 *vs.* 51 years in COMPERA and REVEAL respectively), range of the international normalized ratio (1.5 to 2.5 in REVEAL and 2.0 to 3.0 in COMPERA) and the type of enrolled patients (Primarily prevalent patients in REVEAL whereas COMPERA had only incident patients) and usage of parenteral prostanoids.

In the REVEAL registry a higher percentage of patients (46%) were on intravenous or subcutaneous prostanoids along with warfarin as compared to only 2% in the COMPERA registry. Antiplatelet effects of these parenteral prostanoids results in lesser thrombotic events in the IPAH cohort which might have reduced any added beneficial effect of warfarin in the REVEAL registry even after statistical methods to adjust for the influence of other PAH medications in the outcome. Two-year survival in the COMPERA and REVEAL cohorts not treated with warfarin was 81% versus 89% and 3-year survival was 66% versus 81% respectively. A more aggressive combination PAH therapy in the warfarin treated COMPERA cohort improves the 2-year survival to 89% *vs.* 81% in the cohort not treated with warfarin.

Another reason for the difference between the two registries in the IPAH cohort may be due to immortal time bias in the COMPERA registry. In the COMPERA, those patients who never initiated warfarin because of death due to nonthrombotic causes were compared with those who were initiated warfarin in the study which could have skewed the analysis in favor of warfarin cohort.

The survival curve of patients initiating warfarin in the REVEAL registry matches to that of those not initiating warfarin. A major group of patients (75%) stopped warfarin during the study period as it was poorly tolerated according to the authors, however such high discontinuation rate make the results skeptical. The authors used a time-varying covariate to examine the longitudinal effect of warfarin use due to high discontinuation rates, which would yield comparable results to that of other analytic methodology.

The conflicting results and methodological issues regarding the efficacy of warfarin in IPAH in previous observational studies, meta-analysis as well as in the COMPERA and REVEAL registries needs to be further ascertained by randomized control trials. However, it seems impossible for conducting such trials in PAH due to the complex logistics and lack of industry funding for a less common disease as this. But it is evident that warfarin is no more useful in connective tissue disease associated PAH. Since the final word is yet to be told regarding the survival benefit of warfarin in IPAH, it may be concluded that there

is insufficient evidence to recommend warfarin in these patients except for a small subgroup of patients at greater risk of thromboemboli, long term immobility, chronic indwelling central catheters and low cardiac output state.

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Footnote

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