Letter by Nikpour et al Regarding Article, “Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)”

To the Editor:

We read with interest the article by Preston et al1 reporting the results of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) study of warfarin treatment in pulmonary arterial hypertension (PAH).1,2 We note the investigators’ conclusions that there was no survival advantage observed with warfarin treatment in patients with idiopathic PAH and that warfarin was associated with poorer survival in systemic sclerosis PAH.

Although in the Discussion the authors refer to 8 previous observational studies evaluating the role of anticoagulation in PAH, we note that a key reference by Ngian et al3 was omitted from the article itself and its accompanying editorial. Because this is 1 of only 4 observational studies (including REVEAL) to evaluate the role of anticoagulation with warfarin in systemic sclerosis PAH (n=104; of whom 30% were anticoagulated) and the only study to show a survival benefit (multivariable hazard ratio for mortality, 0.20; 95% confidence interval, 0.05–0.78, P=0.02), even after adjustment for PAH severity and concomitant advanced PAH therapy, we believe that its inclusion is important in presenting a more balanced discussion of this contentious area.

We advise caution in relation to change in treatment practices based on observational data alone. These studies are not designed to systematically capture detailed data on anticoagulation including duration and timing of anticoagulation, target international normalized ratio, stability of international normalized ratio, adverse bleeding outcomes, and their relationship to the intensity of anticoagulation. In addition, clinical features that may influence whether an individual patient is commenced on anticoagulant therapy are not captured or adjusted for. Based on the published studies to date, we believe there now exists a state of equipoise in relation to the role of anticoagulation in both idiopathic PAH and systemic sclerosis PAH that mandates resolution through randomized, controlled trials. The availability of novel anticoagulants such as apixaban and rivaroxaban, offering more predictable bioavailability and stable anticoagulant effects without the need for routine international normalized ratio monitoring, now presents a unique opportunity to evaluate the role of anticoagulation in the management of PAH. The Systemic Sclerosis Pulmonary Arterial Hypertension Intervention with Apixaban (SPHiNX) study (ACTRN12614000418673; NHMRC APP1062638) is an Australian-based, investigator-led multicenter, blinded, randomized, controlled trial of anticoagulation with thromboprophylactic dose apixaban versus placebo as an adjunct treatment in systemic sclerosis PAH that is currently recruiting participants. Once completed, this study is anticipated to shed more light on the role of anticoagulation in this serious and potentially fatal disease. In light of the observed lack of benefit with the use of anticoagulation in idiopathic PAH reported by Preston et al, contrasting the findings of the large Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry, a strong case could be made for a similar randomized clinical trial in patients with idiopathic PAH.4

Disclosures

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