Response to Letter 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)”

We thank Nikpour et al for highlighting their observational, retrospective study, which suggested, in a multivariate analysis, that anticoagulation of at least 6 months was associated with improved survival in connective disease–associated pulmonary arterial hypertension (PAH). Their results, indeed, are contrary to our US-based (Registry to Evaluate Early and Long-Term PAH Disease Management [REVEAL]) and the EU-based (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [COMPERA]) databases, both of which suggested lack of (or even possible harm with) anticoagulation in this high-risk population. Acknowledging that these analyses are limited by the lack of randomization, the study by Ngian et al also suffers from several flaws: lack of definition of survival analysis (start at entry in the database, initial diagnosis, or warfarin start); timing of initiation of anticoagulation (at diagnosis, at entry into the database, or later); level of anticoagulation achieved (international normalized ratio); and length of treatment with anticoagulation and tolerability. We also noted that most patients receiving warfarin were receiving combination therapy for PAH, another independent variable in the study by Ngian et al that was associated with improved survival. Most importantly, the lack of information on the start of warfarin therapy raises the possibility of immortal time bias, an issue also raised in the data from the COMPERA report.

By examining only new warfarin starts, applying the comprehensive REVEAL score to account for disease severity, and detailing the level (international normalized ratio) and length of anticoagulation, we believe our study accounted for many of the possible confounding factors that limit a database analysis.

Acknowledging the unanswered questions and limitations of all the reports to date regarding chronic anticoagulation therapy in connective disease–associated PAH, we commend Nikpour et al on initiating a prospective, randomized, placebo-controlled clinical trial using one of the newer, nonwarfarin anticoagulants.

While awaiting the results of this study, we believe that the weight of current evidence strongly implies that warfarin is potentially detrimental in patients with connective disease–associated PAH and that it should not be used in these patients in the absence of strong indications, such as documented thromboembolic disease.

Disclosures

Dr Preston has served as a consultant for Actelion Pharmaceuticals, Bayer, Gilead, and United Therapeutics; has received research grants from Actelion Pharmaceuticals, Bayer, Gilead, and United Therapeutics; and has received consulting fees from Actelion Pharmaceuticals, United Therapeutics, Bayer, and Ikaria; and has served on a speaker’s bureau or given presentations on behalf of Actelion Pharmaceuticals, Gilead, and Bayer. Dr Roberts reports no conflicts.

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