Correspondence

Anti-coagulation in pulmonary arterial hypertension: the real blood and guts

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We read with interest the "Perspective" by Cirulis *et al.* and the accompanying editorial by Pakshirajan, both of which discuss our recent publication analyzing the effect of anticoagulation with warfarin in patients with pulmonary arterial hypertension (PAH) enrolled in the REVEAL registry (1).

The REVEAL registry is a US-based multicenter cohort and the largest database to date of patients with group I PAH. Analysis of the REVEAL database "revealed" information contrary to multiple historical reports suggesting that anticoagulation is beneficial to patients with PAH. Despite enrolling 3,500 patients and tracking them for 5 years, REVEAL suffers from the inherent limitations of any registry. Yet, it and the European-based PH registry COMPERA have both queried our current recommendations about anticoagulation in PAH patients (2). Although the observations from REVEAL and COMPERA are congruent in some forms of PAH [no benefit in connective tissue disease (CTD)-PAH], they are conflicting in others [idiopathic PAH (IPAH)]; thus, they do not provide incontrovertible direction for the clinician.

Based on these observations, what should we do today? For patients with CTD-associated PAH, the answer is clear: there are no data suggesting a positive effect of warfarin. Moreover, recent information (especially with scleroderma patients) suggests a detrimental outcome. However, the issue remains controversial for patients with IPAH: should we anti-coagulate these individuals?

The conflicting data generated over the past 40 years can only be truly rectified by a randomized clinical trial evaluating the effect of anti-coagulation in PAH patients. Whether this will ever occur is problematic (we think it is highly unlikely). But if it did occur, what would be the ideal design?

First, and foremost, it would include IPAH patients. Patients with drug-induced PAH and hereditary PAH could also be considered, as their characteristics and outcomes mirror IPAH. The trial would be randomized, placebo-controlled, double-blinded, and would require multiple centers. Because we lack robust surrogate markers for long-term outcomes in PAH, the primary endpoint would have to be the most difficult to use in a PAH trial: survival.

Prostacyclins have anticoagulant properties due to the effect on platelet aggregation. In addition, they are generally reserved for the sicker, more advanced patients. Therefore, stratification based on exposure to prostanoids would be advisable.

One interesting difference between COMPERA and REVEAL was the exposure time to warfarin. US patients did not seem to tolerate warfarin as well as European patients: in REVEAL, at 3 years only a third of patients were still taking the drug, while in COMPERA, the patients had a much better retention time and rate. Thus, one might speculate that part of the lack of effect in REVEAL may have been due to the insufficient time on warfarin. As such, the trial would make every effort to choose a drug that is well-tolerated.

Given these considerations, would the newer, direct anticoagulants (DOACs) be more appropriate drugs to study in PAH? DOACs have proven efficacy and safety in a host of cardiovascular disorders, as both prevention and treatment (3). Their mechanisms of action include direct

thrombin inhibition and factor Xa inhibition. The main advantages over traditional anticoagulants, such as warfarin, include a lower overall mortality, mainly due to fewer episodes of fatal intracranial bleeding (4) and lack of need for blood monitoring. However, they are not a panacea, since they are contraindicated in patients with significant renal impairment and in obese patients. If the PAH community ever embraces, by necessity, this very long, survival trial, it seems to us that DOACs may best fit the profile of the appropriate agent. In fact, a trial evaluating the efficacy and safety of apixaban in scleroderma-associated PAH is currently underway in Australia (5); its primary endpoint is time to clinical worsening in this high risk population.

In conclusion, use of anticoagulation has become more controversial in patients with PAH. We, as clinicians, have the duty to inform our patients of the conflicting evidence, and as researchers, to advance knowledge in this area by resolving the issue with evidence-based medicine.

Although PAH is a rare disease, the recently concluded long-term, event-driven randomized trials, SERAPHIN (6), AMBITION (7), and GRIPHON (8), enrolled over 500 patients each, suggesting that long-term, large clinical trials in PAH are in fact feasible.

In sum, we are making an appeal to the international PH community to design and perform a large multi-national trial that would finally clarify the role of anticoagulation in patients with PAH.

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Footnote

Conflicts of Interest: Dr. Farber is a member of the Steering Committee of the REVEAL Registry which was funded by Actelion. Dr. Preston has no conflicts of interest to declare.

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