Whither Anticoagulation in Pulmonary Arterial Hypertension? Conflicting Evidence REVEALed

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Despite the availability of a burgeoning array of therapies for pulmonary arterial hypertension (PAH), including agents targeting the prostaglandin, endothelin, and nitric oxide pathways, long-term outcome remains of concern. Providers therefore seek to leverage every possible advantage in the battle to prolong the lives of these compelling patients. Historically, that effort has included the use of warfarin, which is based on the pathophysiological concepts of the potential role of in situ thrombosis or superimposed thromboemboli in disease progression and buttressed by early nonrandomized analyses of factors affecting patient outcome. Warfarin anticoagulation has been such a dogmatic component of the approach to PAH that the precarious evidence base on which it rests may be underestimated. In this issue of Circulation, an analysis from the Registry to Evaluate Early and Long-Term Disease Management in PAH (REVEAL) appears to have further eroded the rather wobbly legs of that base. The REVEAL registry is the largest PAH registry ever developed and has been mined for an astonishing array of useful analyses, including the changing demographics of PAH, temporal trends of treatment and outcome, and development of prognostic tools. This registry owes its success to a highly motivated collaborative team, dedicated and sophisticated statistical support, and proper funding. However, registry-based forays into the analysis of the impact of specific treatment on outcome are of course fraught with well-known hazards. Statistical methods can to some extent correct for known confounders such as disease severity, but other confounders may be unknown or difficult to take into account (eg, disease trajectory and patient compliance). However, in the persisting absence of randomized trials of anticoagulation in PAH, registry-based analyses remain the best available source of information in this regard.

To put this analysis in perspective, it is valuable to consider the details of the early evidence supporting warfarin use in PAH and to consider what conditions must be met in the current era for warfarin to be effective in improving PAH survival. First, in situ thrombosis or thromboemboli must occur. Second, this process must have sufficient adverse impact (either gradual or abrupt) on coupling of the right ventricle to the pulmonary circulation to contribute to irretrievable, fatal progression of right ventricular failure. Third, warfarin must be effective in reducing thrombotic processes. Fourth, warfarin must be adequately tolerated and used in a fashion sufficient to reduce thrombotic processes. Finally, the risk of warfarin use must be more than offset by its protective effects.

To what extent is thrombosis part of the pathophysiology of PAH progression? Can patients be risk stratified with regard to the potential for thrombosis to contribute to their deterioration? We know relatively little about these critical points, particularly in the modern treatment era. However, the early autopsy studies of pulmonary vascular disease are worth revisiting. The landmark Heath-Edwards classification system was based primarily on pulmonary vascular changes occurring in congenital heart disease but included 2 cases of primary pulmonary hypertension. In the distal distended sac of the plexiform lesions characteristic of grade 4 vasculopathy, “there is frequently a thrombus.” In the seminal Wagenvoort and Wagenvoort examination of 156 cases submitted under the diagnosis of primary pulmonary hypertension, 31 seemed pathologically to be better classified as chronic thromboembolic pulmonary hypertension, and of those, about half in retrospect had clinical features that could have suggested that diagnosis antemortem. So, if it is still true that a subgroup of patients classified as idiopathic PAH (IPAH) in fact have undetected thromboembolic pulmonary hypertension, the use of warfarin may improve their outcome, hence the critical nature of the systematic use of ventilation perfusion lung scans to search for these hidden patients, particularly if warfarin use in patients classified as IPAH diminishes. Interestingly, in patients with pathologically proven “vasoconstrictive” pulmonary hypertension (what we now call IPAH), Wagenvoort and Wagenvoort found only “an occasional small organized thrombus” in most lungs, but in 6 patients, “thromboembolic lesions were more numerous and mixed with vasoconstrictive alterations. This may indicate that primary pulmonary hypertension was complicated by thrombosis or thromboembolism.” Accordingly there may be a subset of IPAH patients in whom thrombosis plays a greater role and for whom warfarin may be more likely to be useful; they may be lost within the larger cohort.

The extent to which thrombosis plays a role in the progression of PAH in the current era and whether the use of parenteral prostanooids affects this role are largely unknown. This
deserves further study, is yet another reason supporting efforts to halt the slide in autopsy rates, and is a call for systematic analysis and reporting of the pathological findings in lungs explanted at time of lung transplantation.

The early clinical evidence for anticoagulation in PAH is also worthy of reconsideration. A single-center, retrospective analysis of outcome of 120 patients is an important component. It is relevant to note that the 1-year survival in that study cohort was low (70% overall; 80% for those receiving warfarin, 60% for those not receiving warfarin), largely reflecting the absence of targeted vasodilator therapy in that era. Despite efforts to exclude known thromboembolic pulmonary hypertension from that cohort, 18% of the subgroup who underwent autopsy had findings most consistent with chronic thromboembolic pulmonary hypertension based on thrombus in both elastic and muscular arteries and did not appear to have “primary plexogenic arteriopathy.” Efforts to confirm the benefits of warfarin in the autopsy-proven plexogenic subgroup were impeded by the smaller number of such patients. However, it was noted that 39% of the patients who underwent autopsy had only small muscular arteries containing thrombi, including fresh platelet-fibrin thrombi, perhaps representing either microemboli or in situ thrombosis and supporting the concept of warfarin and antiplatelet approaches in such patients who otherwise seemed to meet criteria for what we now call IPAH. A subsequent prospective, nonrandomized study of factors influencing PAH outcome that examined 64 patients who were challenged with calcium channel blockers and continued on them if they responded added support to the anticoagulation concept. Both those who responded to calcium channel blockers and those who did not respond appeared to benefit from warfarin, although most of the difference in survival was driven by superior outcome in the calcium channel blocker nonresponders treated with warfarin compared with the calcium channel blocker nonresponders who did not receive warfarin. The survival difference between nonresponders who received warfarin and those who did not was huge: 91% versus 52% at 1 year. Interestingly, the decision to use warfarin in this study was based on abnormal perfusion lung scans—an early example of an effort toward individualized medicine—and raised the question of the pathophysiological correlate of the abnormal perfusion studies. As a result of these studies, the use of warfarin in PAH became well accepted, worked its way into the guidelines, and was even extrapolated to patients with PAH related to the scleroderma spectrum of disease.

However, the use of warfarin incurs risk and inconvenience. Keeping a patient within the targeted therapeutic range is difficult; drug interactions are common; and as right ventricular failure progresses, liver congestion may make the degree of anticoagulation increasingly labile. Systemic prostanoids have antiplatelet activity and may be associated with thrombocytopenia. Patients with the scleroderma spectrum of diseases may have gastrointestinal telangiectasia, further increasing the risk of bleeding. As efforts begin to expand therapies into the realm of antiproliferative, proapoptotic, antiangiogenic, and anti-inflammatory pathways, there is potential for off-target effects that may unexpectedly enhance the risk of cerebral hemorrhage. Accordingly, the need for more data has been long-standing, and that need is beginning to be met.

In 2014, the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) contributed additional important information about the role of anticoagulation. COMPERA enrolls patients from 7 European countries, although >80% of subjects to date have been enrolled from German centers, so COMPERA reflects primarily German treatment patterns. Two thirds of IPAH patients in this registry received anticoagulation compared with 43% of those with connective tissue disease associated with PAH. A significant benefit for warfarin use was found for the idiopathic cohort, whereas there was a trend toward worse outcome for the connective tissue disease cohort.

The REVEAL analysis also found that patients with scleroderma-associated PAH who initiated warfarin had an increased hazard for death (unadjusted hazard ratio, 2.03, \(P=0.03\); REVEAL risk score–adjusted hazard ratio, 1.60, \(P=0.15\)) compared with those who did not.

This result is concordant with the COMPERA analysis. It is fair to conclude that there is no available evidence supporting the use of warfarin in scleroderma-associated PAH. Indeed, it may be harmful.

However, the REVEAL analysis did not detect benefit for warfarin in IPAH, in contradistinction from COMPERA. How do we explain this difference, and what are the implications? As the authors of the REVEAL analysis point out, there are major differences between these registries in both the characteristics of enrolled patients and the treatment patterns. The mean age of patients in the REVEAL analysis is 51 years compared with a median age of 68 years in COMPERA. REVEAL patients are primarily prevalent, whereas COMPERA only enrolled incident patients. The goal international normalized ratio in North America is typically 1.5 to 2.5, whereas 2.0 to 3.0 is usual in Europe. Of IPAH patients starting warfarin in REVEAL, 46% were on intravenous or subcutaneous prostanoids (compared with only 15% who did not receive warfarin), whereas in COMPERA, only 2% were on prostanoids at study entry. The number of patients in COMPERA who initiated parenteral prostanoids during follow-up is not reported but is believed to be substantially lower than in REVEAL. Given the antiplatelet effects of parenteral prostanoids, it is conceivable that patients receiving parenteral prostanoids are at lower risk for thrombotic events and therefore less likely to benefit from warfarin, although sensitivity analysis in REVEAL in an effort to adjust for effects of PAH medication still did not suggest benefit for warfarin. Survival at 2 and 3 years in the COMPERA cohort not treated with warfarin was considerably worse than in the corresponding REVEAL cohort (2-year survival of 81% and 3-year survival of 66% in COMPERA versus 89% and 81%, respectively, in REVEAL). The 2-year survival in the warfarin-treated COMPERA cohort was 87%. A more aggressive overall treatment approach in the COMPERA warfarin cohort compared with the cohort not receiving warfarin, supported by more frequent use of combination therapy in the warfarin cohort, could amplify the differences in outcome. Efforts to adjust for that effect did not detect such an interaction, but fully adjusting for such founders is difficult. The REVEAL authors also cited potential for immortal time bias in COMPERA. In COMPERA, patients initiating warfarin in the study were compared with
those who never initiated warfarin. It is possible that some of those patients never initiated warfarin because they died of nonthrombotic causes before having the opportunity to do so rather than dying because they were not on warfarin. This would skew the analysis to favor the warfarin cohort. An additional analysis of the COMPERA data set could be performed to obviate this concern.

Inspection of the survival curve of patients initiating warfarin in REVEAL (Figure 2 in the article) demonstrates an early hazard of death (10% within 6 months), followed by a plateau more closely tracking the outcome of patients not initiating warfarin. Despite admirable efforts to match and correct for disease severity, it is possible that the initiation of warfarin in a primarily prevalent cohort signaled recognition of the deteriorating trajectory in previously stable patients and at times represented part of a “Hail Mary” approach rather than a pre-emptive strategy. This potential difference in disease trajectory may represent a confounder not fully accounted for by matching for REVEAL risk score. An additional concern about the findings of the REVEAL analysis revolves around the fact that fully 75% of patients treated with warfarin had the medication stopped during the period of observation. If discontinuation rates were this high in a clinical trial, the results would be highly suspect. However, the authors used a time-varying covariate to examine the longitudinal effect of warfarin use, accounting for warfarin starts and stops, with this sensitivity analysis yielding results comparable to the results of alternative analytic methodology. The sophistication of this methodology is impressive. The frequent cessation of warfarin in the REVEAL analysis led the authors to conclude that “warfarin was poorly tolerated.” This is speculative; it could also be speculated that, instead of warfarin being poorly tolerated, the enthusiasm for warfarin use in PAH in North America is dwindling.

Given the conflicting results of COMPERA and REVEAL with regard to warfarin anticoagulation in PAH, what are we to conclude? The usual response would be to call for randomized trials. However, the prospects for that actually occurring seem rather dim, given the generic standing of warfarin and the complex logistics of a large clinical trial in PAH for which no industry funding can be expected. Much effort was put into developing a National Institutes of Health grant to study this topic, which unfortunately ran into the headwinds of what were at the time exquisitely tight funding lines (personal communication, David Badesch, MD, University of Colorado). Perhaps a trial of one of the novel anticoagulants could be performed, although the interest of the pharmaceutical industry in funding anticoagulation studies in a less common disease compared with other conditions such as atrial fibrillation is likely limited.

We are now left with major uncertainty about the role that warfarin should play in IPAH in the modern era. The following seem reasonable to consider. First, if there are relative contraindications (noncompliance with international normalized ratio monitoring, highly labile international normalized ratio values, bleeding diathesis, desire for active sports in which warfarin use may be hazardous, etc), warfarin should be avoided. Second, if warfarin use in IPAH diminishes, the luxury of not worrying about whether thrombosis or emboli may be contributing to patient deterioration will be lost. When we see a patient with progressive right ventricular failure and a climbing pulmonary vascular resistance, in the absence of warfarin therapy, we will need to think about that. Perhaps doing a ventilation/perfusion lung scan periodically or even studying serial ventilation/perfusion lung scans or computed tomography angiograms in IPAH patients with or without warfarin treatment would be valuable. Third, there may be subgroups of patients in whom warfarin may be more likely to be valuable: patients at greater risk of thromboemboli as a result of venous congestion, immobility, risk of thrombus forming on chronically indwelling central lines particularly if patent foramen ovale is present, lower cardiac output, and higher pulmonary vascular resistance. Ultimately, we are left in a discomfitingly common state in the world of PAH: exercising our best clinical judgment, considering individual patient circumstances, and seeking better data wherever we can find them.

Disclosures
Dr Frantz has participated in advisory board and steering committee roles with Actelion without personal financial gain aside from coverage of travel expenses for attendance.

References

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