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Pulmonary Vascular Resistance in Pulmonary Arterial Hypertension: La Pièce de Résistance?

To the Editor:

We read the recent manuscript by Badagliacca and colleagues with great interest (1). In this Italian multicenter retrospective cohort of 181 treatment-naive patients with pulmonary arterial hypertension (PAH), they evaluated the relationship between change in pulmonary vascular resistance (PVR) following initiation of dual oral combination therapy and two widely used approaches for multidimensional risk assessment (2, 3). Failure to achieve treatment goal (i.e., a low-risk profile using the French method or a REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management] 2.0 score <7) was related to smaller reductions or increases in PVR with initial therapy across baseline risk groups. They developed a weighted score using baseline variables to predict an inadequate PVR reduction with initial dual oral combination therapy. This score consisted of male sex, age ≥ 60, and two interaction terms of *1*) mean pulmonary arterial pressure ≥ 48 mm Hg with cardiac index <2.5 L/min/m^2 and *2*) echocardiographic right ventricular area/left ventricular area >1 with a tricuspid annular plane systolic excursion <18 mm.

This study provides new support for the clinical relevance of medication-induced changes in PVR. We recently advocated for the use of risk profiles as clinical trial endpoints (4). The change in PVR and/or a PVR prediction score could very well be integrated into such multidimensional endpoints if their findings are replicated. As they did not analyze survival or whether the weighted PVR prediction score added predictive value to multidimensional risk scores for anticipating clinical outcomes, further validation of their findings in a larger cohort is necessary. However, this study complements our recent work demonstrating that the relative change in PVR from baseline and absolute value of PVR obtained at first follow-up right-heart catheterization were important predictors of long-term survival in large cohorts with idiopathic, heritable, and drug-induced PAH (5) and systemic sclerosis–associated PAH (6). We wished to underscore the importance of considering relative PVR changes together with objective measures of right ventricular function, as some patients may still significantly improve PVR but with deteriorating right ventricular function, which portends a poor prognosis (7).

We have three main comments. First, given the variables in their weighted PVR prediction score, we are curious why the authors chose to add their score to REVAL 2.0, as there are inherent redundancies of variables in their prediction model (age >60 and male sex) within the REVEAL 2.0 score (3). Although they show incremental improvement in the performance of their models, we wondered if there is significant multicollinearity between these variables. If so, it could have resulted in overfitting and make their models less generalizable outside this relatively small cohort.

Second, we wished to commend the authors on demonstrating for the first time the important sex differences in risk scores achieved after initial treatment. Male patients were less likely to improve to low risk and more likely to be in intermediate risk at follow-up, which is possibly explained by the greater improvements in right ventricular function observed in females. Given worse outcomes in males with PAH, dual combination therapy may be inadequate for many men, and a sex-specific strategy may be warranted. However, more between-sex comparisons in Table E4 regarding age, etiology, smoking prevalence, spirometry, and diffusion capacity would be important, as these risk factors for atypical PAH, or the so-called pulmonary vascular phenotype in smoking-related lung disease (8), could have partially explained the inferior responses in men.

Lastly, Badagliacca and colleagues highlight the near certainty of treatment failure with dual oral combination therapy in high-risk patients, as none improved to low risk in their study (1). This reinforces the notion of initial triple combination therapy, including a parenteral prostacyclin for high-risk patients, consistent with previous observational studies (9, 10) and the treatment algorithm proposed in the sixth World Symposium on Pulmonary Hypertension (11). ■

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Reply to Weatherald *et al.*

From the Authors:

We thank Weatherald and colleagues for their supportive comments, and pleasant reminiscence of French cuisine, on our recent report on risk reduction and hemodynamics after initial dual combination of therapies in pulmonary arterial hypertension (1). We fully agree on the importance of pulmonary vascular resistance combined with imaging of the right heart, as there may be dissociation (2), although this is unlikely when pulmonary vascular resistance decreases by more than 50–60% (3). Their other points are also well taken. *1*) Redundancies in pulmonary arterial hypertension risk scores easily occur, as most parameters of prognostic relevance are inevitably related to right ventricular function. We could indeed have acknowledged this with greater clarity. *2*) Sex differences in risk scores are of great clinical relevance in relation to the greater capacity of the female right ventricle to adapt to increased afterload, as recently reemphasized (4). *3*) The inevitable failure of initial dual-combination therapy in high-risk patients strongly argues in favor of their treatment with initial triple-combination therapies.

We like to add that not only initial high-risk patients fail and that the definition of a high-risk status may vary greatly from one score to another. Over half of treated patients actually remain with poor prognosis intermediate or high-risk status whatever the scoring system. This calls for earlier and more intensive combination therapies with parenteral prostanoids and more intensive follow-up with repetitive right heart catheterizations and imaging modalities (5). ■

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