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When "AMBITION" Isn't Good Enough: Risk Status and Dual Oral Therapy in Pulmonary Arterial Hypertension

In 2015, the AMBITION (The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial permanently altered the landscape of pulmonary arterial hypertension (PAH) therapy by demonstrating conclusively the efficacy of upfront dual oral therapy (1). However, despite examining multiple primary and secondary clinical endpoints, AMBITION did not include any cardiopulmonary hemodynamic metrics as an endpoint (1). In this issue of the *Journal*, Badagliacca and colleagues (pp. 484–492) retrospectively examined the effect of initial dual oral therapy with an ERA (endothelin receptor antagonist) and PDE5i (phosphdiesterase type 5 inhibitor) (predominantly ambrisentan and tadalafil) on pulmonary vascular resistance (PVR) and risk-assessment score in 181 patients newly diagnosed with PAH (2). Risk-assessment scores were calculated using the simplified European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines score and the REVEAL 2.0 risk-assessment tool (3, 4). Superficially, their results support the conclusions published in the AMBITION trial—therapy was well tolerated, and, on average, patients demonstrated significant improvements in World Health Organization functional class, 6-minute-walk distance, PVR (−40.4%), mean pulmonary artery pressure (mPAP), right atrial pressure, cardiac index (CI), and several echocardiographic parameters; moreover, the magnitude of the decrease in PVR did correlate with outcome (1, 2). In addition, the authors found that starting in low-risk status was associated with maintaining low-risk status on dual oral therapy at follow-up (19/27 remained low risk by ESC/ERS, 11/19 by REVEAL 2.0) (2).

However, on closer examination, the picture is far less rosy. Only a minority of patients actually achieved low-risk status at follow-up: 43.1% by ESC/ERS and even fewer by REVEAL 2.0 (34.8%). Furthermore, only ∼50% of patients at intermediate risk on presentation improved to low-risk status, and none of the high-risk patients improved to low risk at follow-up, with almost 50% remaining high risk. Only 7.7% normalized their PVR, whereas 10.5% demonstrated progression despite therapy. Notably, several factors were associated with poor PVR response, including age >60, male sex, baseline mPAP >48 mm Hg with low CI, and an elevated right ventricle (RV) to left ventricle (LV) ratio (RV/LV) with low tricuspid annular plane systolic excursion (TAPSE) by echocardiography (2).

The conclusion is unmistakable: In a disconcerting majority of patients, dual oral therapy is simply not good enough. In fact, even in the original AMBITION trial, only a minority of patients (39%) demonstrated a "satisfactory clinical response" at 6 months (1) despite being on dual oral therapy under optimal conditions. Furthermore, it has been well demonstrated that persistence of high-risk status is associated with poor outcomes (5). Yet despite this, current recommendations from the World Symposium on Pulmonary Hypertension 2018 recommend an initial trial of dual oral therapy for non–high-risk patients, with transition to triple combination therapy in intermediate- or high-risk patients on follow-up (3). However, there are a number of studies demonstrating persistently poor outcomes even if parenteral therapy is employed as the rescue maneuver (6, 7). As a result, it has been suggested that this approach may be too little too late (8). The results of the current study support this conclusion, demonstrating in a "real-world" setting that for the overwhelming majority of patients not deemed low risk at initiation of therapy, dual oral therapy is inadequate as an initial treatment strategy.

There is a sound physiologic rationale for this conclusion. As has been repeatedly shown, RV dysfunction is a strong predictor of outcomes in PAH (9). PVR is a surrogate measure of RV afterload in PAH. It is therefore not surprising that in the present study, PVR reduction was tightly associated with improvement in risk status (2). As such, adequate upfront reduction of PVR should be the primary goal of initial therapy. Though dual oral therapy is clearly beneficial, it just does not achieve timely or sufficient reduction of PVR in the majority of patients.

This conclusion leaves us seeking more aggressive upfront treatment strategies. Although triple oral add-on therapy has been employed with incremental benefit in prevalent patients (10), in the recently concluded TRITON (The Efficacy and Safety of Initial Triple versus Initial Dual Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension) trial investigating triple upfront combination oral therapy, all primary and secondary endpoints (similar to those in this study) were negative (11). In contrast, in two small, uncontrolled studies with different—albeit much sicker—incident cohorts, triple upfront therapy regimens with a systemic prostanoid had robust hemodynamic and clinical effects (12, 13). In addition to the

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aforementioned studies, there is clear evidence demonstrating the ability of parenteral therapy to lower PVR; in fact, parenteral therapy, even when employed as monotherapy, can attain far greater improvements in PVR than was demonstrated in the present study. Akagi and colleagues demonstrated the efficacy and tolerability of high-dose intravenous epoprostenol monotherapy in lowering PVR (by 68%), which markedly outstrips the improvements noted here (14). In addition, there is evidence to suggest that rapid uptitration of intravenous epoprostenol (with presumed concurrent lowering of PVR) also improves outcomes in comparison with gradual uptitration (15). As such, these observations strongly suggest we reevaluate the role for parenteral therapy.

Unfortunately, aggressive, high-dose, upfront parenteral therapy is not without its drawbacks. Side effects—both uncomfortable and dangerous—can occur, and line-associated complications as well as quality-of-life issues abound, making it critical to identify those patients in whom early, more aggressive therapy might be most beneficial.

It is here that the present study offers potential guidance. A "PVR score" was created based on age, sex, mPAP + CI, and RV/LV ratio with TAPSE. In combination with either of the risk calculators (ESC/ERS or REVEAL 2.0), the authors generated two scoring systems predictive of a poor PVR response to dual oral therapy, with improved discrimination in the low- and intermediate-risk groups (2). By identifying those patients at high risk of a poor PVR response, more aggressive treatment (including parenteral therapy) could be instituted early, when it is potentially most beneficial.

Methods such as these have the ability to begin the journey to more personalized therapy in patients newly diagnosed with PAH. With development of more specific genetic profiling by PVDomics, newer therapies that exploit alternate and/or proliferative pathways in PAH (i.e., sotatercept), and better risk-assessment tools (i.e., REVEAL 2.0 LITE), we are poised to take an exciting step toward truly personalized medicine in PAH (5, 16, 17). Think about a future in which patients undergo thorough risk profiling and genetic testing before beginning upfront therapy with two-, three-, or even four-drug regimens (any of which might be parenteral). Only through such an approach can we cease gambling on an initial response and instead make significant strides in the treatment of this otherwise deadly disease. ■

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