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Lessons from the COMPASS-3 Study

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As treatment options for pulmonary arterial hypertension (PAH) have evolved, clinicians now face the enigma of both which medication(s) should be started and which parameters should be followed to dictate our selection of treatment. Although a number of treatment goals have been described in PAH,[1] 6-min walk distance (6MWD) has remained one of the most widely used measures in both PAH pivotal trials as well as in clinical practice. The Phase-4 multicenter COMPASS-3 study published in this issue of *Pulmonary Circulation*[2] sought to evaluate whether using a singular endpoint of 6MWD $\geq$ 380 m produced clinically meaningful outcomes in PAH. This study was conducted during 2007–2010, i.e. before publication of recent guidelines as well as longer-term clinical trials evaluating combination therapy.

Outcomes were assessed for 100 newly diagnosed PAH patients following a treat to target strategy. All patients received bosentan monotherapy for the initial 16 weeks. This was followed by combination therapy with add-on sildenafil for those who did not achieve a 6MWD $\geq$ 380 m, while patients who reached the target walk distance continued on bosentan monotherapy. Very few patients (16/100) achieved the 6MWD target at 16 weeks. Long-term clinical worsening rates were similar between patients meeting the $\geq$ 380 -m distance at 16 weeks and those who did not. After the 16-week time point, the 76 patients who had not reached $\geq$ 380 m received add-on sildenafil, and 15 out of 76 patients then reached the target 6MWD by week 28.

The second part of the paper focused on prognostic measures in PAH more generally. A number of measures were predictive, particularly at 16 weeks (versus fewer at baseline), including 6MWD, NT-proBNP level, hemodynamics, and cardiac MRI measures including right ventricular end diastolic volume: left ventricular end diastolic volume (RVEDV:LVEDV) ratio, right ventricular ejection fraction, and stroke volume, among others. In the multivariate testing, NT-proBNP plus age provided a good model at both baseline and at 16 weeks, with similar predictive power to models with more variables. In the combined model that also included "change-in" variables, the combination of RVEDV:LVEDV ratio (baseline) and change in pulmonary vascular resistance (PVR) was felt to provide the best statistical model.

The retention of change in PVR in the final model is interesting, as PVR is often excluded from multivariate models because authors either exclude it outright due to the potential for multicollinearity or it is not retained in the model after stepwise testing. However, a recent large prognostic study from the French Pulmonary Arterial Hypertension Network registry found that out of all of the hemodynamic measures tested, post-treatment RA pressure and PVR led to the most predictive model when using Akaiki Information Criteria for model selection, though stroke volume, cardiac index, and compliance were all significant predictors when added individually in place of PVR.[3]

The final section of the paper looked at correlations between hemodynamics and cardiac magnetic resonance imaging (MRI) measures. The strongest correlation was found between RVEDV:LVEDV ratio and PVR, mean pulmonary arterial pressure and PVR index. These results add to a growing literature showing that both NT-proBNP and cardiac imaging may be important prognostic measures. It is particularly valuable to see strong results for cardiac MRI from a multicenter study. Criticisms, however, include the relatively large number of measures tested and the fairly small number of outcome events for this type of analysis (i.e. 2/16 monotherapy patients [13%] and 15/76 combination therapy patients [19%, P = NS]).

Returning to the walk distance analysis in the current study, the other important walk distance finding was the very modest additional improvement when sildenafil was added to bosentan – this combination yielded a median absolute 6MWD improvement of only 10 m at week 28, while the group remaining on monotherapy had a median 3-m decrease between weeks 16 and 28. Although we suspect that much of this relates to limitations in the efficacy of current PAH therapy (especially given relatively modest improvements with add-on therapy in other trials[4,5]), there are several other potential contributors. One concern is that this particular drug combination could be less effective, potentially due to a drug–drug interaction. Bosentan is known to decrease serum sildenafil concentrations by up

to 50%, and this could have a significant impact on efficacy of this combination.[6,7] Indeed, the addition of bosentan to sildenafil in the COMPASS-2 study only led to a mean improvement in 6MWD of 7.2 m.[8,9] COMPASS-3 may also have included patients with more risk factors for HFpEF, as evidenced by the median BMI of 29.3 (range = 14.5–47.4 kg/m^2), older age of 57.5 years (range = 21–84 years), and perhaps somewhat more lenient inclusion–exclusion criteria, potentially also contributing to the results.

This study also raises several methodology questions. The authors utilized a "treat to target" strategy and found no difference in the monotherapy group versus the step-up combination therapy group. However, the lack of randomization as well as the marked differences in baseline clinical characteristics of the two groups make this comparison difficult to interpret. The relatively short follow-up time (52 weeks) and the low overall number of clinical events (time to clinical worsening and/or decline) may also contribute, leading to a significantly under-powered study. Nevertheless, the focus on treatment strategy is an interesting and important one, given the costs and potential adverse reactions that come with increasing polypharmacy. Few PAH studies have focused on therapeutic strategies, with the main exception being the recent AMBITION study,[9] which compared upfront combination therapy with ambrisentan and tadalafil compared to monotherapy with one or the other. Combination therapy was clearly more effective, even in lower-risk patients, and is now a recommended consideration for initial therapy in most patients.[1,9]

An alternative comparison that could be considered for future study would be upfront combination therapy compared with a "step-up" strategy that starts with monotherapy alone. If this type of trial is to be completed, choice of endpoint will also be important. Meta-analyses of randomized controlled trials and other studies in PAH have also suggested that change in 6MWD may not explain a large proportion of the treatment effect and is not a good surrogate endpoint for mortality.[10] On the other hand, it has also served the PAH field well as a simple, easy-to-measure test of exercise capacity (an important component of PAH symptoms), and it has allowed smaller sample sizes with studies of shorter trial duration than would have been needed for time to event type trials. Most likely, we will continue to see 6MWD utilized as an endpoint in PAH studies, particularly in the earlier phases of development, but we feel 6MWD alone would not be ideal as a measure or target for assessing the long-term efficacy of PAH therapy strategies.

In summary, in the COMPASS-3 study, 6MWD $\geq$ 380 m did not serve as a clinically meaningful prognostic indicator when used in combination with a strategy of step-therapy with bosentan and sildenafil for the treatment of PAH. However, this study does support the use of cardiac imaging and NT-proBNP as important prognostic markers in PAH and the use of combinations of prognostic markers to make treatment decisions. Future studies focused on different treatment strategies in PAH are needed in order to better direct clinical practice.

Conflict of interest

Dr. Chin reports reimbursement for work on steering committees and advisory boards for Actelion and United Therapeutics and research support through grants to her institution from Actelion, Bayer, the NIH, SoniVie and United Therapeutics. Dr Shah has received research support through grants to his institution from Actelion Pharmaceuticals, Bayer Pharmaceuticals, and National Institutes for Health (NIH). Dr Shah has also served on speakers' bureau and advisory board for Gilead Sciences.

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