Impact of left heart disease risk factors on risk stratification and treatment response in pulmonary arterial hypertension

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Background: Contemporary registries have documented a change in the epidemiology of PAH patients displaying increasing co-morbidities associated with left heart disease (LHD). These patients are often excluded from randomized clinical trials. It is unclear whether the presence of LHD comorbidities may adversely impact the accuracy of risk stratification and response to PAH therapy.

Method: Data was extracted from the Pulmonary Hypertension Society of Australia and New Zealand registry for incident patients with a diagnosis with idiopathic/heritable/toxin-induced (I/H/D)-PAH and connective tissue disease (CTD) associated PAH from 2011 - 2020. Patients without available medication and follow up data were excluded. We used the AMBITION trial exclusion criteria to define the subpopulation with LHD risk factors and haemodynamic phenotype (PAH-rLHD).

Results: 489 patients (I/H/D-PAH=251, CTD-PAH=238) were included in our analysis, with 103 (21.0%) fulfilling the definition of PAH-rLHD (34 had $\geq$3 risk factors for left heart disease (rLHD-hypertension, diabetes, obesity or ischaemic heart disease) and 76 had borderline haemodynamics (mean capillary wedge pressure 13–15 with pulmonary vascular resistance $<$500 dynes sec/cm^5) including 7 who met both criteria). Compared to classical PAH, patients with PAH-rLHD were older at diagnosis (66±13 vs 58±19, p$<$0.001), had lower pulmonary vascular resistance (PVR: 393±266 vs 708±391, p=0.031) but worse exercise capacity (6MWD: 286±130m vs 327±136m, p=0.005). PAH-rLHD were more likely to be started on initial monotherapy, compared with "classical" PAH (73% vs 56%, p=0.002). In the monotherapy groups, endothelin receptor antagonists (ERA) were used in 73% PAH-rLHD, compared with 66% in classical PAH group. Both groups exhibited similar response to both mono- and combination therapy with commensurate improvements in WHO functional class (mean change 0.3±0.6 vs 0.3±0.8, p=0.443) and 6-minute walk distance (mean change 44±82 vs 48±101, p=0.723). There was no difference in survival between classical PAH and PAH-rLHD (log rank, p=0.29). The REVEAL 2.0 risk score effectively discriminated risk in both populations at baseline and first follow up (classical PAH: baseline C statistic 0.750, follow up 0.774 and PAH-rLHD: baseline C statistic 0.756, follow up 0.791).

Conclusion: Despite lower PVR at diagnosis, PAH-rLHD patients and "classical" PAH demonstrate similar response to first-line therapy with similar long term survival. The REVEAL 2.0 risk score can be effectively applied to the subpopulation of PAH-rLHD in real life clinical practice.