

Composite clinical worsening endpoint in Paediatric PAH - clinically meaningful and feasible for clinical research

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Introduction: Clinical worsening (CW) composites are used in adult Pulmonary Arterial Hypertension (PAH) clinical research and is in discussion for future use in paediatric PAH research across all age ranges.

Methods: This study, using data from the Tracking-Outcomes-in-Paediatric-Pulmonary-Hypertension (TOPP) registry, describes the occurrence of individual outcomes and its CW composite: death, lung transplantation (LT), PAH-related hospitalisation (i.e. increased right heart failure, hemoptysis), atrial septostomy, deterioration in WHO functional class(FC) (change in 1 FC), initiation of parenteral prostanoids, syncope, PAH worsening (i.e. occurrence/progression of at least 2 symptoms: dyspnea, cyanosis, cough, fatigue, chest pain, dizziness). Predictive Cox proportional hazards models of time to death/LT were conducted for the aforementioned individual outcomes and CW composite (excl. death/transplantation).

Results: 255 incident (diagnosed ≤ 3 months) patients (i.e. idiopathicPAH/familialPAH, PAH associated with congenital heart disease) were included in the analysis. 155 (60%) were female and the mean (\pm SD) age at diagnosis was 7.5 (± 5.2) years; 159 (62%) had iPAH/fPAH; 109 (43%) were in WHO FC II and 87 (34%) in class III. The highest incident rates per 100 person-years (95% CI) were observed for deterioration in WHO FC 24.8 (20.8, 29.5) and PAH related hospitalisation 18.3 (15.0, 22.4). In univariate models, first event of deterioration in WHO FC, (hazard ratio (HR)=6.7; 95% CI 3.1, 14.4), and first occurrence of PAH worsening (HR=4.8; 95% CI 2.5, 9.0) were highly predictive of time to death/lung transplantation. PAH related hospitalisation and initiation of parental prostanoids had similar HRs. The predictive value of the occurrence of syncope did not reach statistical significance. The HR of the CW composite was 2.7 (95% CI 1.4, 5.3). The multivariate predictive models which included all individual variables (all univariate p-values < 0.15) revealed deterioration of WHO FC (HR=3.5; 95% CI 1.5, 8.3), PAH related hospitalisation (HR=2.6; 95% CI 1.3, 5.2) and occurrence of PAH worsening (HR=2.1, 95% CI 1.0, 4.4) to be significant independent predictors of death/LT.

Conclusions: The chosen CW composite as well as the individual components (except syncope) occurred to be predictive for death/LT, thus supports the usefulness for clinical research but also for risk assessment during follow-up in paediatric PAH.