Initial triple therapy in pulmonary arterial hypertension: coming of age and rejuvenated

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A rare condition in children and adults alike, pulmonary arterial hypertension (PAH) is progressive and carries a poor prognosis [1, 2]. Therapeutically, three pathways are being targeted to induce vasodilation, inhibit vascular proliferation and reduce the load on the right heart: the endothelin, nitric oxide and prostacyclin (PGI₂) pathways [3]. Incident adult patients with severe PAH (i.e. with a high, >10% risk of 1-year mortality) are preferably treated with a parenteral PGI₂ analogue, while the double oral combination of a phosphodiesterase type-5 (PDE-5) inhibitor and an endothelin receptor antagonist (ERA) is considered standard of care for most other patients with mild to moderate PAH [1, 2, 4]. On the basis of the landmark AMBITION trial [5], PDE-5 inhibitor/ERA combination treatment is preferably started right after diagnosis (initial combination therapy). One small retrospective study in treatment-naïve, incident patients with severe PAH suggested exceptional benefit from initial triple combination therapy, consisting of a PDE-5 inhibitor, an ERA and intravenous epoprostenol [6]. This result was recently confirmed in a similar observational study of severe incident PAH patients treated with a combination including the subcutaneous PGI₂ analogue treprostinil [7]. The more recently developed prostacyclin receptor (IP) agonist selexipag was shown to improve outcomes in prevalent patients on initial mono- or combination therapy [8]. However, the benefit of initial triple combination therapy in treatment-naïve, mild-to-moderate PAH patients has not been established.