



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

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Initial triple therapy benefits severe PAH patients across the ages <https://bit.ly/3o9vB1G>

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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.

As the treatment algorithm for adult PAH is maturing, there has been much less scientific guidance to decide on the treatment of paediatric PAH patients. Supported by registry data and observational studies, the therapeutic approach in children with PAH is roughly the same as in adult PAH patients. Randomised clinical trials in children with PAH have been rare and results have been much debated. In the STARTS-1 and STARTS-2 studies, children randomised to monotherapy with the PDE-5 inhibitor sildenafil displayed favourable performance and survival, although higher doses were unexpectedly related with increased mortality [9, 10]. No results are available from randomised trials evaluating PGI₂ analogues, IP agonists or ERAs in paediatric PAH. In one of the first observational studies on epoprostenol in PAH, a 13-year-old girl was enrolled who benefited from treatment for several years, until receiving a lung transplant [11].

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Survival benefit of such treatment in children was later confirmed in observational studies [12]. Likewise, a case for oral combination therapy in children with PAH can be made on the basis of observational data. Indeed, registry data suggests that performance and survival are better in children receiving oral combination therapy of an ERA and PDE-5 inhibitor [13, 14]. In this issue of the *European Respiratory Journal*, yet another observational study on the treatment of paediatric PAH is published. HAARMAN *et al.* [15] present the outcome of initial triple combination therapy consisting of a PDE-5 inhibitor, ERA and parenteral PGI₂ analogue in a cohort of 21 children with different forms of precapillary pulmonary hypertension. Most children were diagnosed with idiopathic or hereditary PAH; two received a final diagnosis of pulmonary venous occlusive disease. 95% of children were in functional class III or IV. Remarkably, children with idiopathic and heritable PAH showed 1-, 2- and 3-year transplant-free survival estimates of 100%, 94% and 87% [15]. These numbers compare perfectly with the 94–100% survival rates after 2–3 years achieved with triple therapy in adult severe PAH [6, 7]. Since this was not a formal interventional trial and a Potts shunt was created in about half of the children, the data is somewhat difficult to interpret. However, the uniqueness of the observations and the exceptionally good survival rates attained in such severe cases of paediatric PAH make this publication of great value. Obviously, important unresolved questions remain. First, there is the important possibility of selection bias: why were these children eligible for triple therapy whereas others were not? Second, could similar results have been achieved with double (oral) combination therapy or monotherapy, whether or not in conjunction with the creation of a Potts shunt? However, as the authors point out, there is little chance that a randomised trial will ever be performed in this category of patients.

A number of important lessons can be learned from this study. First, this is the third independent report of excellent outcomes in severe PAH when using aggressive initial triple therapy. The accumulation of favourable results in observational studies is of major importance, as it is ethically debatable to conduct a proper randomised study to evaluate this strategy. In addition, what should be the comparator in such a trial? Following the guidelines, it should be the combination of epoprostenol and one oral drug. Recent data from the French Registry showed that initial triple combination therapy provided survival benefit over double combination of epoprostenol and one oral drug [16]. Comparison with initial oral dual combination therapy would be ethically questionable. The second lesson learned from the work of HAARMAN *et al.* [15] is that pharmacological treatment of children with drugs that were rigorously tested only in adult PAH patients seems justified. No major complications were reported with any of the three classes of drugs that seem specific for the paediatric PAH population. The unexpected results on survival with high-dose sildenafil from the previously reported STARTS trials remain unexplained, but it was suggested that other factors were influencing the survival comparisons in that study. No deaths were considered to be treatment related, and the majority deaths were related to PAH in children receiving monotherapy only [9, 10]. Likewise, ERAs and PGI₂ analogues seem to have no specific side-effects in children. The final message in the HAARMAN *et al.* [15] report is that surgical creation of a Potts shunt deserves further evaluation, particularly in children with PAH, but perhaps in (young?) adults with PAH as well. The fact that this procedure is not without risk is illustrated by the fact that creation of the shunt resulted in the perioperative death of one child. However, while most surviving children without a Potts shunt were in a similar good clinical condition at last follow-up, there were some indications of possible benefit from the shunt: follow-up time since diagnosis was substantially longer in those who underwent a Potts procedure and parenteral PGI₂ therapy was stopped in five out of six children with a Potts shunt *versus* two out of seven children without a Potts shunt. In recent years, several reports were made of prolonged survival and long-lasting improvement in functional capacities in children and a few young adults with severe, drug-refractory PAH [17–20]. Aggregated evidence provides some guidance for optimal selection of patients for either surgical or percutaneous creation of a Potts shunt, and criteria for eligibility include therapy refractory PAH, supra-systemic pulmonary artery pressures and a relatively preserved right heart function [21]. Technical expertise is another essential requirement and it therefore seems obvious that performance of the procedure remains reserved to a few selected centres world-wide. Fortunately, an international registry has been set up to compile the data from 14 expert centres around the globe [21].

In conclusion, the observational study by HAARMAN *et al.* [15] is yet another piece of evidence in favour of initial triple combination therapy in severe PAH. This strategy seems not only beneficial in adults, but also in children with severe PAH. As evidence from randomised clinical trials will probably never be generated, initial triple combination therapy including a parenteral PGI₂ analogue should be considered standard of care in severe PAH, whether it is in children or adults. The add-on benefit of the creation of a Potts shunt in selected patients deserves further study.

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