Pediatric pulmonary arterial hypertension

Towards optimal classification, treatment strategies and outcome

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General introduction and outline of the thesis

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) can occur as a symptom of a heterogeneous spectrum of diseases and is defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg, measured invasively during cardiac catheterization.[1] It is classified into five subgroups based on pathological, pathophysiological, clinical and therapeutic similarities (updated clinical classification of pulmonary hypertension, Nice, France, 2013, Table 1).[2] Group 1 represents pulmonary arterial hypertension (PAH). PAH can be idiopathic (IPAH), hereditary, drug and toxin induced or associated with an underlying condition. Associated conditions include connective tissue disease, human immunodeficiency virus, portal hypertension, congenital heart diseases (CHD) and schistosomiasis. Group 2 to 5 represent PH due to left heart disease, PH due to lung diseases and/or hypoxia, chronic thromboembolic PH and PH with unclear multifactorial mechanisms, respectively. In contrast to the other four groups, PAH is a progressive and intrinsic disease of the small pulmonary arteries that is characterized by unique vascular neointimal lesions.[3] In PAH, elevated mPAP and pulmonary vascular resistance lead to increased right ventricular workload. This results in right ventricular hypertrophy and dilatation, and eventually in right ventricular failure and death.

PATHOBIOLOGY OF PAH

Although the pathobiology of PAH is not completely understood, endothelial dysfunction is believed to play a key role.[3,4] This dysfunction is associated with an imbalance of pulmonary vasodilators and vasoconstrictors that are produced by the pulmonary endothelial cells. This leads to a decreased production of pulmonary vasodilators, which also have anti-proliferative effects, and an increased production of pulmonary vasoconstrictors, which also have proliferative effects. In the past decades, three major pathways contributing to this imbalance have been identified: the prostacyclin, endothelin-1 and nitric oxide (NO) pathways.[5] Endothelin-1 is a potent vasoconstrictor with proliferative effects on vascular smooth muscle cells.[6] Levels of endothelin-1 are increased in patients with PAH.[7] Prostacyclin and NO on the other hand are vasodilators with anti-proliferative effects.[3] Remodeling of the small pulmonary arteries involves smooth muscle cell, endothelial cell and fibroblast proliferation and leads to obstructive and plexiform lesions. Furthermore, inflammation and thrombosis are thought to play a role in the development of PAH.[3]

Table 1. Updated classification of pulmonary hypertension, Nice, France, 2013

1	**Pulmonary arterial hypertension (PAH)**
1.1	Idiopathic PAH
1.2	Heritable PAH
1.2.1	BMPR2
1.2.2	ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3	Unknown
1.3	Drug and toxin induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″	Persistent pulmonary hypertension of the newborn (PPHN)
2	**Pulmonary hypertension due to left heart disease**
2.1	Left ventricular systolic dysfunction
2.2	Left ventricular diastolic dysfunction
2.3	Valvular disease
2.4	Congenital/acquired left heart inflow/outlow tract obstruction and congenital cardiomyopathies
3	**Pulmonary hypertension due to lung diseases and/or hypoxia**
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental lung diseases
4	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
5	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3	Metabolic disorders: glycogen storage disorders, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR, bone morphogenic protein receptor II; CAV1, caveolin-1; ENG, endoglin; HIV, human immunodeficiency virus.

TREATMENT OPTIONS IN PAH

Before the 1990s there were only supportive therapies for PAH including anticoagulants, oxygen and diuretics. Since then several drugs have become available that mainly lead to vasodilatation. The first class of drugs that became available for the treatment of PAH were the calcium channel blockers (CCBs). Unfortunately, CCBs are only effective in a small percentage of patients.[8,9] Therefore, there was a high need for the development of other drugs. In the mid-1990s the first PAH-targeted drug, epoprostenol, became available.[10] Epoprostenol is a synthetic prostacyclin and a potent vasodilator. Thereafter, several other drugs targeting the prostacyclin pathway became available, togheter with drugs targeting the endothelin-1 and NO pathways: the endothelin receptor antagonists and type 5 phosphodiesterase inhibitors, respectively.[11,12] As the PAH-targeted drugs target three different pathways, combination therapy may be beneficial since these drugs could have a synergetic effect.

If PAH progresses despite maximal medical therapy, several interventions, such as balloon atrial septostomy or Potts shunt, may be indicated to preserve cardiac output and improve right ventricular loading conditions.[13-15] Ultimately, a lung (or heart-lung) transplantation might be the only option.[16,17]

PEDIATRIC VERSUS ADULT PAH

PAH occurs both in adults and children. Although similarities between adult and pediatric PAH exist, there are also important differences between these two groups regarding associated conditions, clinical presentation and prognosis.[18-20] For example, PAH in adults is frequently associated with connective tissue disease, whereas this subgroup is rare in children. PAH-CHD often presents with more complex CHD in children than in adults. Furthermore, extracardiac comorbidities, such as genetic or congenital anomalies, are much more frequent in children than in adults and are believed to affect disease evolution and progression.[21-23] Growth and developmental anomalies, including in-utero factors and maladaptation to postnatal life, may play a modifying role in pediatric PAH.[19,24,25] These, for pediatric PAH unique, factors are currently insufficiently acknowledged in the clinical classification of PH.[2] Growth and different developmental stages may also affect pharmacokinetics and –dynamics of targeted drugs, which could impact drug safety and efficacy and lead to the need for different dosing regimens or drug formulas in children.[26] Thus, findings in adult PAH cannot be simply extrapolated to pediatric PAH. Sadly, another important difference between adult and pediatric PAH is the scarcity of available data. In adults, efficacy and safety of the PAH-targeted drugs have been evaluated in randomized controlled trials (RCTs) and based on these RCTs,

evidence-based guidelines have been developed.[1] To date, such advances are delayed in pediatric PAH. Therefore, adult data are often extrapolated to children and pediatric treatment strategies are mostly based on adult data or experience of pediatric PAH clinicians.

PEDIATRIC PAH

In children, IPAH has been reported to have an incidence rate of <1 case per million children and a prevalence rate of 2 to 4.5 cases per million children.[27,28] IPAH is a diagnosis of exclusion, meaning that all other possible causes for P(A)H first have to be excluded.[1] In recent years, advances in genetic diagnostic tools revealed several genes to be involved in the pathogenesis of PAH, of which a mutation in the bone morphogenetic protein receptor type 2 is the most frequent. Consequently, part of patients that were first classified as IPAH are now known to have hereditary PAH and are therefore also classified as such.

The incidence rate of PAH-CHD is slightly higher compared to IPAH and has been reported to be 2.2 cases per million children.[27] CHD is the most common birth defect and has an incidence of approximately 1% worldwide.[29] It varies from simple septal defects to complex cardiac malformations. Increased pulmonary blood flow, through a left-to-right shunt, has been recognized to trigger molecular and cellular changes in the pulmonary vasculature leading to progressive PAH.[30] The risk for developing PAH and its pace of progression highly depend on the anatomical location and size of the shunt-defect.[31-33] For example, almost all patients with a post-tricuspid shunt-defect, if unrepaired, develop PAH in the first years of life while only 10-15% of patients with a pre-tricuspid shunt-defect develop PAH in the 3rd or 4th decade of life. PAH can also occur after adequate shunt-closure and has been reported in non-shunt CHD, such as aortic coarctation and transposition of the great arteries corrected with arterial switch operation in the neonatal period.[21,27] Thus, PAH-CHD in itself represents a heterogeneous subgroup of PAH. It becomes even more heterogeneous as extracardiac comorbidities, such as Down syndrome, genetic traits and congenital anomalies, are frequent in this group.[22] Currently, PAH-CHD can be further classified according to the updated clinical classification of PAH-CHD, which is based on the presence or history of a shunt-defect and which was proposed for both adults and children at the 5th World Symposium on PH in Nice, France, 2013 (Nice-CHD-classification, Table 2).[2]

Table 2. Updated clinical classification of pulmonary arterial hypertension associated with congenital heart disease, Nice, France, 2013

1	**Eisenmenger syndrome** Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.
2	**Left-to-right shunts** – Correctable – Non correctable Include moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.
3	**Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease** Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects is contraindicated.
4	**Post-operative PAH** Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/ develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is aggressive.

OUTCOME AND IMPROVING OUTCOME IN PEDIATRIC PAH

PAH has a poor prognosis. In untreated adults with PAH, median survival has been estimated to be 2.8 years and this is thought to be even worse in children with PAH.[34] Since the introduction of the PAH-targeted drugs and the implementation of evidence-based treatment guidelines, quality of life and survival of adults with PAH has strongly improved.[35,36] Survival of children with PAH seems to have improved also but remains unsatifactory.[37-41] Furthermore, reported survival rates differ significantly between studies, which may be due to differences in patient selection and inclusion criteria but which may also be a consequence of different treatment and follow-up strategies adopted by the reporting centers.[37-41] To improve the currently unsatisfactory survival in pediatric PAH and to strive to optimal outcome, there are, to date, several unmet needs. Since there is no cure for PAH, optimal outcome includes both prolonging life and improving or maintaining quality of life.

Firstly, information on the expected disease course and pace of disease progression in the individual child is essential. Disease progression may differ between subtypes of PAH. For instance, it has been reported that children with PAH-CHD have better outcome than children with IPAH although similar outcome has also been reported.[38-40] Furthermore, different types of CHD may lead to different outcomes in both children and adults with PAH-CHD.[27,38,42,43] Although the Nice-CHD-classification was recently shown to identify subgroups with specific disease characteristics and outcomes in adults[44], data regard-

ing the value of this classification in pediatric PAH are currently lacking. Next to type of PAH, disease severity at moment of diagnosis plays an important role in prognosis, i.e. children with worse clinical and hemodynamic characteristics at diagnosis have worse prognosis. Many clinical and hemodynamic parameters have been suggested to predict outcome in pediatric PAH but their prognostic value differs between studies. Thus, there is a need for the identification of robust predictors of outcome.

Secondly, optimizing treatment strategies is a major need in pediatric PAH. For the development of evidence-based treatment guidelines, RCTs are essential. However, the design and execution of pediatric RCTs is hampered by several problems, including the rareness and heterogeneity of PAH in children.[24] Another major issue is the lack of a validated clinically meaningful parameter that could serve as primary endpoint in pediatric RCTs.[24] The six-minute walk distance has been used in most pivotal RCTs in adult PAH[11,12,45] but its use in children is limited since it cannot be performed in young or developmentally restricted children. Therefore, there is a high, and to date unmet, need for such an endpoint that is suitable in children of all ages. Next to determining drug efficacy, knowing how to use these drugs is essential, i.e. when and how to start and escalate therapy and what doses to use. Data regarding this issue are very limited in pediatric PAH. Currently, a more aggressive and goal-oriented treatment strategy is being adopted in both adult and pediatric PAH.[1,17] In such a strategy, specific treatment goals should be reached and otherwise therapy is escalated. Clinical or hemodynamic parameters, that predict outcome and can be influenced by therapy, may serve as treatment goals to determine whether children are optimally treated or need escalation of therapy.

AIMS AND OUTLINE OF THE THESIS

Although survival of children with PAH seems to have improved since the introduction of the PAH-targeted drugs, prognosis remains unsatisfactory. To optimize outcome in pediatric PAH, optimal classification of this heterogeneous disease and the identification of robust predictors of outcome may help to provide risk stratification and assessment in the individual child. In addition, optimal treatment strategies, including timing, dosing and escalation of PAH-targeted therapies and the use of combination therapy, are key. To optimize treatment strategies, the development of a clinically meaningful endpoint that could be used in pediatric RCTs is essential.

Therefore, the aims of this thesis are:

1. To characterize the subgroup of pediatric PAH-CHD including evaluation of the Nice-CHD-classification.
2. To describe current treatments and treatment strategies and to assess their effect on outcome in pediatric PAH.
3. To describe survival of pediatric PAH in the current era of PAH-targeted drugs and to identify predictors of outcome.
4. To assess the value of a candidate clinical endpoint, i.e. physical activity measured by accelerometry, in pediatric PAH.

Chapter 2 focuses on pediatric PAH-CHD, a very heterogeneous subgroup of PAH. Adequate risk assessment and stratification in the individual child are highly needed, which may be provided by a clinical classification. To date, pediatric data regarding the value of the recently proposed Nice-CHD-classification are lacking. We describe phenotypic heterogeneity in pediatric PAH-CHD and assess whether the Nice-CHD-classification reflects differences in patient and disease characteristics and survival.

Chapter 3 describes the concurrence of childhood PAH and transposition of the great arteries repaired with arterial switch operation in the neonatal period. Although rare, this concurrence is well recognized in pediatric PH centers. Nevertheless, a clinical characterization is lacking. We present an international cohort, including several national registries from Europe and a major referral center for pediatric PAH from the United States, of children with this association and describe its epidemiology and clinical course.

Chapter 4 provides an overview of current and advancing (non-)drug treatments for PAH and the limited pediatric efficacy and safety data. Furthermore, it discusses the use of goal-oriented treatment strategies, the (lack of) pediatric data regarding treatment goals used in these strategies and the high need for validated treatment goals and clinical endpoints in pediatric PAH.

Chapter 5 focuses on children treated with intravenous and subcutaneous (IV/SC) prostanoids, which are potent vasodilators. In pediatric PAH, IV/SC prostanoids are frequently used and form a part of established therapy in children with advanced PAH. However, data regarding dosing, timing, discontinuation or transition to oral/inhaled therapies are limited. Furthermore, reported doses differ significantly between studies. We report current clinical practice regarding the use of IV/SC prostanoids in pediatric PAH including a detailed description of transition to oral/inhaled therapy, used doses and outcome.

Chapter 6 provides a systematic review with meta-analysis of reported prognostic parameters in pediatric PAH. Several studies have recently reported on survival and prognostic factors in pediatric PAH but these studies are mostly based on relatively small cohorts and report contradictory findings. As prognostic parameters could be used for risk stratification in the individual child and given the high clinical need for improving treatment strategies and developing treatment guidelines in pediatric PAH, we identify, appraise, synthesize and combine currently available data on this issue.

In **Chapter 7** we present a contemporary cohort of consecutive pediatric PAH patients seen in three major referral centers in the Netherlands and United States between 2000 and 2010. Survival of pediatric PAH patients seems to have improved compared to historical reports but reported survival rates differ significantly. Differences in patient inclusion and study design hamper direct comparison of these reported survival differences. However, these differences may reveal important information on clinical predictors of survival and the optimal treatment strategy. Using similar standardized inclusion criteria, we directly compare patient characteristics, treatment strategies and outcome, and identify predictors of outcome in this transatlantic cohort.

In **Chapter 8** a new candidate clinical endpoint for pediatric PAH is evaluated: physical activity measured by accelerometry. In pediatric PAH, the development of evidence-based treatment guidelines is hampered by a lack of RCTs. An essential problem in pediatric trial design is the lack of a validated clinically meaningful endpoint applicable in the pediatric age spectrum. Although accelerometry has been proposed as potential endpoint in pediatric PAH because of its feasibility in young children, data regarding accelerometry are lacking in this population. We compare physical activity measured by accelerometry in children with PAH to that in healthy controls and assess whether accelerometer output correlates with disease severity and outcome in children with PAH.

Chapter 9 provides a general discussion of the results of this thesis.

Chapter 10 provides a English and Dutch summary of the results of this thesis.

REFERENCES

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS): Endorsed by: Association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
3. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):13S-24S.
4. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest. 2008;118(7):2372-2379.
5. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351(14):1425-1436.
6. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res. 2004;61(2):227-237.
7. Yoshibayashi M, Nishioka K, Nakao K, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. evidence for increased production of endothelin in pulmonary circulation. Circulation. 1991;84(6):2280-2285.
8. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
9. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: Occurrence and prognostic value when comparing three response criteria. Eur Heart J. 2011;32(24):3137-3146.
10. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296-301.
11. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148-2157.
12. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896-903.
13. Micheletti A, Hislop AA, Lammers A, et al. Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension. Heart. 2006;92(7):969-972.
14. Blanc J, Vouhe P, Bonnet D. Potts shunt in patients with pulmonary hypertension. N Engl J Med. 2004;350(6):623.
15. Baruteau AE, Serraf A, Levy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: Long-term results. Ann Thorac Surg. 2012;94(3):817-824.
16. Lammers AE, Burch M, Benden C, et al. Lung transplantation in children with idiopathic pulmonary arterial hypertension. Pediatr Pulmonol. 2010;45(3):263-269.
17. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
18. Rosenzweig EB, Widlitz AC, Barst RJ. Pulmonary arterial hypertension in children. Pediatr Pulmonol. 2004;38(1):2-22.
19. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: A comparison between children and adults. Eur Respir J. 2011;37(3):665-677.

20. Berger RM, Bonnet D. Treatment options for paediatric pulmonary arterial hypertension. Eur Respir Rev. 2010;19(118):321-330.
21. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
22. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: Complex presentation and diagnosis. J Pediatr. 2009;155(2):176-82.e1.
23. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.
24. Berger RM. Pulmonary hypertension: Smaller kids, smaller steps. Lancet Respir Med. 2014;2(5):348-350.
25. Hopper RK, Abman SH, Ivy DD. Persistent challenges in pediatric pulmonary hypertension. Chest. 2016;150(1):226-236.
26. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: The FUTURE-1 study. Br J Clin Pharmacol. 2009;68(6):948-955.
27. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
28. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
29. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-1900.
30. Berman EB, Barst RJ. Eisenmenger's syndrome: Current management. Prog Cardiovasc Dis. 2002;45(2):129-138.
31. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. Circulation. 1968;37(5):805-815.
32. Tulloh RM. Congenital heart disease in relation to pulmonary hypertension in paediatric practice. Paediatr Respir Rev. 2005;6(3):174-180.
33. van Albada ME, Berger RM. Pulmonary arterial hypertension in congenital cardiac disease--the need for refinement of the evian-venice classification. Cardiol Young. 2008;18(1):10-17.
34. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. results from a national prospective registry. Ann Intern Med. 1991;115(5):343-349.
35. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation. 2002;106(12):1477-1482.
36. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J. 2005;25(2):244-249.
37. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(4):697-704.
38. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
39. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
40. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.

41. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
42. Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. factors relating to deterioration and death. Eur Heart J. 1998;19(12):1845-1855.
43. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in eisenmenger syndrome: A combined retrospective and case-control study. Eur Heart J. 2006;27(14):1737-1742.
44. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: A comparison between clinical subgroups. Eur Heart J. 2014;35(11):716-724.
45. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132(6):425-434.

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Clinical classification in pediatric pulmonary arterial hypertension associated with congenital heart disease

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ABSTRACT

Background– Congenital heart disease (CHD) is a frequent cause of pediatric pulmonary arterial hypertension (PAH), with diverse etiology and outcome. We aimed to describe phenotypic heterogeneity in pediatric PAH associated with CHD (PAH-CHD), assess the applicability of the Nice-CHD-classification, and explore whether this classification accurately reflects patient/disease characteristics and survival.

Methods– All children with CHD from a contemporary cohort of consecutive pediatric PAH patients followed in three major referral centers (Denver, New York, the Netherlands) were characterized and classified on the basis of the latest proposed clinical classification for PAH-CHD (World Symposium on Pulmonary Hypertension, Nice, France, 2013).

Results– According to this classification, 24% of 134 children were classified into group 1, 14% into group 2, 19% into group 3 and 30% into group 4; 11% could not be classified. Types of CHD and hemodynamic profile differed between groups, with the highest right atrial pressure in group 4 ($p<0.040$). Group 3 children had Down syndrome less frequently ($p=0.011$) but other (un)defined syndromes most frequently ($p=0.063$) and received most intense PAH-targeted therapy ($p=0.003$). With 15 deaths and one lung transplant (12%; median follow-up: 4.3 years), survival differences could not be demonstrated between the groups in the Nice-CHD-classification.

Conclusions– Pediatric PAH-CHD is a heterogeneous condition frequently associated with extracardiac, developmental factors that are believed to affect disease development. The Nice-CHD-classification identifies groups with specific patient/disease characteristics. However, a substantial proportion of children could not be classified. Group 3 forms a distinct disease entity. Its prognostic value could not be determined because of the low number of events. The Nice-CHD-classification supports clinical characterization of PAH-CHD; however, further refinement is needed to classify all children with PAH-CHD.

INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect and comprises a broad spectrum of defects, varying from simple septal defects to complex cardiac malformations.[1] Pulmonary arterial hypertension (PAH), a progressive disease of the pulmonary vasculature, is an important determinant of morbidity and mortality in CHD patients.

PAH associated with CHD (PAH-CHD) is a heterogeneous disease. Increased pulmonary blood flow, through a left-to-right shunt, has been recognized to trigger molecular and cellular changes in the pulmonary vasculature, leading to progressive PAH.[2] The risk of developing PAH and its pace of progression highly depend on the anatomical location and size of the shunt-defect.[3-5] In patients with CHD and early-stage pulmonary vascular disease (PVD), shunt closure can reverse and resolve PAH.[6,7] In time, PAH will pass a point of no return and becomes irreversible. Shunt closure is then contraindicated, as it is believed to worsen prognosis. PAH has also been reported in non-shunt CHD, such as aortic stenosis or coarctation.[7-9]

In some children, advanced PAH concurs with CHD that is considered not sufficient to explain the PAH.[10] For example, pre-tricuspid shunts usually cause PAH from the third decade of life. Sometimes, severe PAH may be observed already in young children with such a shunt. In children with CHD, coexisting extracardiac factors may not only complicate clinical presentation but also increase susceptibility for developing PAH and thus play a modifying role.[10] These include chromosomal or syndromal abnormalities, but also developmental lung/airway anomalies and metabolic diseases.

Consequently, there is a need for adequate risk assessment and stratification in the individual child, which might be provided by a clinical classification for PAH-CHD. Such a classification would be most useful when it allows for identification of patient groups with specific disease characteristics, risks, or outcomes that allow tailored treatment approaches. Recently, an updated shunt-related classification was proposed for both adults and children at the Fifth World Symposium on Pulmonary Hypertension in Nice, France, in 2013 (the Nice-CHD-classification).[11,12]

Survival of both adults and children with PAH-CHD has been reported to be associated with the type of CHD.[7,13,14] In adults, the value of the Nice-CHD-classification regarding differences in disease severity and survival between groups was recently reported.[15] Although pediatric PAH-CHD has been evaluated with classifications based on hemodynamic relevance or anatomical location of the shunt-defect, data regarding the Nice-CHD-classification in children are currently not available. We aimed to describe phenotypic heterogeneity in children with PAH-CHD, to assess the applicability of the Nice-CHD-classification, and to explore whether this classification accurately reflects patient/disease characteristics and survival.

METHODS

Patients

For this study, all children with PAH and CHD were selected from a recently described[9] contemporary cohort of consecutive pediatric PAH patients from the Children's Hospital Colorado in Aurora, the Columbia University Medical Center in New York and the Dutch National Referral Center for Pediatric Pulmonary Hypertension at the University Medical Center Groningen/Beatrix Children's Hospital in the Netherlands. This cohort includes all children with PAH who visited these centers between 2000 and 2010 and had a diagnosis of PAH confirmed by a cardiac catheterization after 1997 at the age of ≥3 months and <18 years. PAH was defined as mean pulmonary artery pressure (mPAP) of ≥25 mmHg, mean pulmonary capillary wedge pressure of ≤15 mmHg and indexed pulmonary vascular resistance (PVRi) of ≥3 Wood units.m^2.

Children with other forms of pulmonary hypertension (PH), such as PH due to left heart disease, lung disease and/or hypoxia or chronic thromboembolic disease, were not included in this cohort. In case of mixed disease, meaning CHD and one of these conditions, it was at the discretion of the treating physician in the referral center, using the information from the cardiac catheterization, to define which was the most explanatory component for the PH: PAH-CHD or PH due to the coexistent condition. Only patients in the former group were included.

In this cohort, children with non-repaired CHD were included only if the CHD was considered inoperable because of advanced PAH. In children with repaired CHD, diagnostic cardiac catheterization was performed more than 1 year after corrective surgery.

During cardiac catheterization, all three centers used the Fick principle to calculate cardiac output and pulmonary blood flow, using either measured or assumed oxygen consumption. In the latter case, oxygen consumption was assumed according to LaFarge and Miettinen[16] (Denver and New York) or Bergstra et al.[17] (Netherlands). In patients with a non-repaired patent arterial duct with right-to-left shunting, cardiac output calculations using Fick were not possible, and such patients are excluded from any analysis.

CHD

The anatomy, physiology and repair status of the CHD were described. Children were classified according to the Nice-CHD-classification (Figure 1). [11,12]

Cyanosis, required for group 1 of the Nice-CHD-classification, was defined as transcutaneous oxygen saturation of <90% at rest. If transcutaneous oxygen saturation was not available, systemic arterial oxygen saturation obtained during cardiac catheterization was used. Also, transcutaneous oxygen saturation of 90%-95% with systemic arterial oxygen saturation of <90% was considered cyanosis. Postductal saturations were used in children with patent arterial duct.

1 Eisenmenger syndrome	Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.
2 Left-to-right shunts	Include moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.
3 Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease	Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects is contraindicated.
4 Post-operative PAH	Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

Figure 1. Updated clinical classification for pulmonary arterial hypertension associated with congenital heart disease, Nice, France, 2013

The distinction between CHD causal for the PAH and PAH with coincidental CHD was based on the expert opinion of the treating physician in the referral center and, for this study, was reviewed and agreed upon by two separate investigators (WMHZ and RMFB). In case of a residual shunt-defect after corrective surgery, the patient was assigned to group 4, postoperative PAH-CHD, only if this shunt-defect was considered not hemodynamically relevant. Otherwise, the patient was classified into group 1 or 2.

Assessments

Patient characteristics included age at PAH diagnosis, sex, and comorbidities. The moment of diagnostic cardiac catheterization, at either the referring or the referral center, was defined as baseline. Disease characteristics at baseline were collected and included both clinical and hemodynamic parameters. Ratios of mean pulmonary-to-systolic artery pressure (mPAP/mSAP) and pulmonary-to-systemic vascular resistance (PVR/SVR) were calculated.

During their disease course, children could receive PAH-specific therapies: calcium channel blocker (CCB) therapy or PAH-targeted therapy consisting of prostanoids, endothelin receptor antagonists, and/or phosphodiesterase 5 inhibitors. Treatment strategy was defined as previously described: CCB monotherapy if CCBs were the only PAH-specific drug used and otherwise the maximum number of PAH-targeted drugs used for at least 3 months or until end of follow-up (PAH-targeted mono-, dual, or triple therapy).[9]

Statistical analyses

Data are presented as mean ± SD, median (interquartile range), or number (percentage) as appropriate. One-way analysis of variance was used to compare normally distributed continuous variables. Non-normally distributed, continuous variables and ordinal variables were compared with the Kruskal-Wallis test. The Chi square and Fisher exact tests were used to compare categorical variables. Post hoc Bonferroni was used to correct for multiple comparisons, as appropriate.

Lung transplantation and death were defined as the primary endpoints. Children who did not die or undergo lung transplantation were censored at the last follow-up visit.

Transplantation-free survival from diagnosis was depicted with Kaplan-Meier curves. To address potential survival bias due to the inclusion of prevalent patients, that is, patients receiving diagnoses between 1997 and 2000, data were left truncated. These patients entered the risk set at their truncation time, which was defined as the time between diagnosis and start of the study. Differences were explored with log-rank tests. A P-value of <0.05 was considered significant.

RESULTS

Patients

In total, 134 children had PAH and CHD (Table 1). Most of these children (77%) had simple pre- or post-tricuspid shunt-defects. Fourteen children (11%) had complex shunt-defects (complete atrioventricular septal defect or non-repaired functional univentricular heart). Seventeen children (13%) had miscellaneous CHD. Thirty-eight percent of the defects were repaired: 31% (n=32) of the simple shunt-defects and 62% (n=8) of the complete atrioventricular septal defects. Most (70%) were repaired within 2 years after birth.

In 60 children (45%) comorbidities were described, most often Down syndrome (n=30). Also, other syndromal abnormalities were reported: Noonan syndrome (n=3), Di George syndrome (n=1), Turner syndrome (n=1), Robinow syndrome (n=1), and undefined syndromes with dysmorphic features, psychomotor retardation, and/or developmental delay of unknown origin (3 children). Coexisting lung abnormalities were reported in 11 children (8%) and included (repaired) congenital diaphragmatic hernia, broncho-pulmonary dysplasia, and chronic lung disease. Other described comorbidities were arteriovenous malformations in the lungs, hereditary telangiectasia, hyperthyroidism, glycogen storage disease 3A, *ABCA3* gene mutation, *ACTA2* gene mutation, Raynaud's phenomenon, rheumatoid arthritis, VACTERL association, and Von Willebrand's disease.

Nice-CHD-classification

Thirty-two children were classified as having Eisenmenger syndrome (ES; group 1), 19 as having PAH associated with left-to-right shunt (group 2), 26 as having PAH with coincidental CHD (group 3), and 40 as having postoperative PAH (group 4; Figure 2). Of the 17 children (13%) with miscellaneous CHD, 2 children with major aortopulmonary collateral arteries could be classified as group 5 PH. The 15 remaining children (11%) could not be classified according to the Nice-CHD-classification.

Table 1. Congenital heart disease in the total cohort

	All (n=134)	Unrepaired (n=83)	Repaired (n=51)
	N (%)	N (%)	N (%)
ASD±PAPVR	28 (21)	22 (79)	6 (21)
VSD and/or PDA	56 (42)	37 (66)	19 (34)
ASD+VSD and/or PDA	19 (14)	12 (63)	7 (37)
Complete AVSD	13 (10)	5 (38)	8 (62)
Non-repaired functional univentricular heart	1 (1)	1 (100)	-
Miscellaneous	17 (13)	6 (35)	11 (65)
Group 5 PH: MAPCAs	2	1	1
Not-classifiable PAH-CHD	15 (11)		
Aortic coarctation	2	0	2
Repaired TAPVR	1	0	1
Unilateral absence of PA	5	4	1
Scimitar syndrome	1	1	0
Neonatally repaired TGA±VSD	6	0	6

Data presented as N (%).

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; MAPCAs, major aortopulmonary collateral arteries; PAPVR, partial anomalous pulmonary venous return; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PDA, patent arterial duct; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; VSD, ventricular septal defect

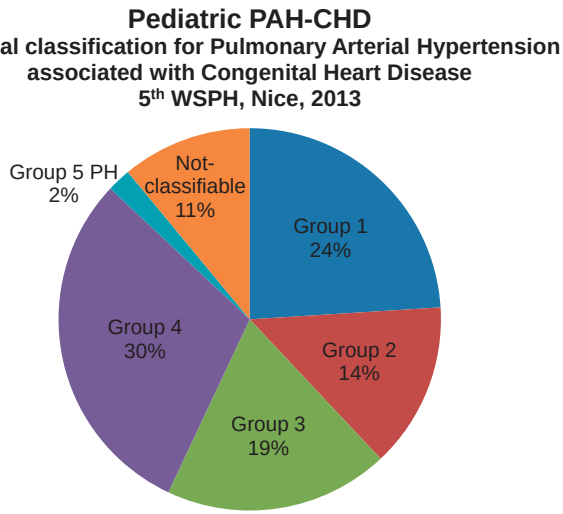

Figure 2. All children classified according to the Nice-CHD-classification

PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; WSPH, World Symposium on Pulmonary Hypertension; PH, pulmonary hypertension.

Within the four groups of the Nice-CHD-classification, age and sex were comparable (Table 2). In contrast, World Health Organization functional class (WHO-FC) tended to differ between the four groups (p=0.066): children with ES had most unfavorable WHO-FC. Also, children with ES had hemodynamic profiles with the highest mPAP/mSAP and PVR/SVR. Cardiac index did not differ between the four groups (p=0.270). Mean right atrial pressure (mRAP) differed between the four groups (p=0.038) and was highest in postoperative PAH. In contrast to children in the other groups, children in group 3 most often had pre-tricuspid shunt-defects (54% vs. 13%-21%, p=0.001). Furthermore, while Down syndrome was less frequent in group 3 (p=0.011), other (un)defined syndromes tended to be more frequent (19% vs. 0%-5%, p=0.063).

In a separate secondary analysis, we compared patients with hemodynamically relevant shunt-defects (groups 1 and 2 combined) with those without such defects (groups 3 and 4 and not-classifiable PAH-CHD; Table 3). Children with hemodynamically relevant shunt-defects tended to have worse WHO-FC (p=0.076) than children without such defects. Furthermore, children with relevant shunt-defects had unfavorable hemodynamics (higher mPAP, PVRi, mPAP/mSAP and PVR/SVR; p<0.020 for these parameters), whereas mRAP was higher in children without a hemodynamically relevant shunt-defect (p=0.031).

Therapy

In total, 117 children (87%) received PAH-targeted therapies during the study period: 51 monotherapy, 43 dual, and 23 triple therapy. Ten children did not receive PAH-specific therapy. Seven children without hemodynamically relevant shunt-defects received CCB monotherapy (1 in group 3, 4 in group 4, and 2 with not-classifiable PAH-CHD).

Treatment intensity differed significantly between the four groups of the Nice-CHD-classification (Table 2; p=0.003). In particular, children in group 3 received PAH-targeted triple therapy more frequently than children in the other groups. Children without a hemodynamically relevant shunt-defect received PAH-targeted triple therapy more frequently than those with a hemodynamically relevant shunt-defect (Table 3; p=0.001).

Not-classifiable CHD

Fifteen children (11%) could not be classified according to the Nice-CHD-classification. This was due to either the absence of a shunt-defect (repaired aortic coarctation [n=2] or corrected transposition of the great arteries with neonatal switch operation [n=6]) or the presence of developmental anomalies of the pulmonary vasculature (including repaired total anomalous pulmonary venous return, absent pulmonary artery, or Scimitar syndrome [n=7]). All children had normal pulmonary capillary wedge pressure (≤15 mmHg).

Table 2. Patient and disease characteristics at baseline stratified by the Nice-CHD-classification and for not-classifiable CHD

	Group 1 (n=32)		Group 2 (n=19)		Group 3 (n=26)		Group 4 (n=40)		Not-classifiable PAH-CHD (n=15)		P-value[a]
	N	Value	N	Value	N		N	Value	N	Value	
Age at PAH diagnosis (years)	32	4.9 (1.5; 11.9)	19	6.8 (4.0; 13.8)	26	3.5 (1.1; 9.4)	40	5.4 (3.0; 12.1)	15	3.9 (2.5; 9.0)	0.268
Female	32	19 (59)	19	16 (84)	26	20 (77)	40	29 (73)	15	7 (47)	0.240
Down syndrome	32	11 (34)	19	4 (21)	26	1 (4)	40	14 (35)	15	0	0.011*†
Cardiac defect	32		19		26		40		NA		0.004*†
ASD±PAPVR		4 (13)		4 (21)		14 (54)		6 (15)			
VSD±PDA		16 (50)		12 (63)		9 (35)		19 (48)			
ASD+VSD and/or PDA		7 (22)		2 (11)		3 (12)		7 (18)			
Complete AVSD		5 (16)		0		0		8 (20)			
Non-repaired functional univentricular heart		0		1 (5)		0		0			
WHO-FC	29		16		21		34		11		0.066
I-II		11 (38)		10 (63)		13 (62)		24 (71)		5 (46)	
III-IV		18 (62)		6 (38)		8 (38)		10 (29)		6 (55)	
mPAP (mmHg)	32	60±13	19	61±20	26	58±21	40	51±17	15	49±18	0.099
mPCWP (mmHg)	32	9±2	19	9±2	26	8±3	40	9±3	15	10±3	0.394
mSAP (mmHg)	32	61±15	19	67±15	26	65±12	39	70±15	15	64±14	0.087
mRAP (mmHg)	31	6±2	19	6±3	25	6±3	40	8±3	13	7±3	0.038‡
PVRi (WU.m^2)	32	17.8±10.5	19	18.5±15.2	26	13.3±9.7	40	13.2±8.6	15	12.0±7.0	0.119
SVRi (WU.m^2)	16	16.8±8.2	17	23.1±14.0	20	19.5±13.7	39	18.8±8.5	13	18.7±7.4	0.407
CI (L/min/m^2)	17	4.1±2.1	19	3.1±1.2	25	3.8±1.4	40	3.8±1.4	15	3.4±1.7	0.270
Qpi (L/min/m^2)	32	4.1±2.8	19	3.8±1.7	26	4.5±1.8	40	4.0±2.0	15	3.6±1.7	0.688
mPAP/mSAP	32	1.00±0.19	19	0.92±0.24	26	0.91±0.37	39	0.75±0.25	15	0.80±0.31	0.002‡
PVR/SVR	16	1.36±0.96	17	0.72±0.25	20	0.71±0.45	39	0.69±0.33	13	0.69±0.34	<0.001*‡§
Treatment strategy	32		19		26		40		15		0.003*‖
No PAH-specific		3 (9)		3 (16)		1 (4)		3 (8)		0	
CCB mono		0		0		1 (4)		4 (10)		2 (13)	
PAH-targeted mono		13 (41)		10 (53)		5 (19)		16 (40)		6 (40)	
PAH-targeted dual		15 (47)		5 (26)		7 (27)		11 (28)		4 (27)	
PAH-targeted triple		1 (3)		1 (5)		12 (46)		6 (15)		3 (20)	

Data presented as N (%), median (interquartile range) or mean ± SD. CCB, calcium channel blocker; CI, cardiac index; mPAP, mean pulmonary artery pressure; mPAP/mSAP, mean pulmonary-to-systemic artery pressure ratio; mPCWP, mean pulmonary capillary wedge pressure; mSAP, mean systemic artery pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PVRi, indexed pulmonary vascular resistance; PVR/SVR, pulmonary-to-systemic vascular resistance ratio; Qpi, indexed pulmonary blood flow; SVRi, indexed systemic vascular resistance; WHO-FC, World Health Organization functional class. For other abbreviations, see Table 1.

[a] P-value only for the four groups of the Nice-CHD-classification (excluding not-classifiable PAH-CHD)
Symbols indicate P<0.05 for indicated comparisons, from a post hoc test with Bonferroni correction: * group 1 and group 3; † group 3 and group 4; ‡ group 1 and group 4; § group 1 and group 2; ‖ group 2 and group 3.

Table 3. Patient and disease characteristics at baseline stratified by the hemodynamic relevance of the shunt-defect

	Hemodynamically relevant shunt-defect (n=51)		No hemodynamically relevant shunt-defect (n=81)		P-value
	N	Value	N	Value	
Age at PAH diagnosis (years)	51	6.1 (1.7; 11.9)	81	4.8 (2.5; 10.1)	0.865
Female	51	35 (69)	81	56 (69)	0.951
WHO-FC	45		66		0.076
I-II		21 (47)		42 (64)	
III-IV		24 (53)		24 (36)	
mPAP (mmHg)	51	60±16	81	53±19	0.019
mPCWP (mmHg)	51	9±2	81	9±3	0.585
mSAP (mmHg)	51	63±15	80	67±14	0.126
mRAP (mmHg)	50	6±3	78	7±3	0.031
PVRi (WU.m^2)	51	18.1±12.3	81	13.0±8.6	0.006
SVRi (WU.m^2)	33	20.1±11.8	72	19.0±9.9	0.623
CI (L/min/m^2)	36	3.6±1.7	80	3.7±1.5	0.628
Qpi (L/min/m^2)	51	4.0±2.4	81	4.1±1.9	0.760
mPAP/mSAP	51	0.97±0.21	80	0.81±0.31	0.002
PVR/SVR	33	1.03±0.75	72	0.70±0.36	0.003
Treatment strategy	51		81		0.001
No PAH-specific		6 (12)		4 (5)	
CCB mono		0		7 (9)	
PAH-targeted mono		23 (45)		27 (33)	
PAH-targeted dual		20 (39)		22 (27)	
PAH-targeted triple		2 (4)		21 (26)	

Data presented as N (%), median (interquartile range) or mean ± SD.
See Tables 1 and 2 for abbreviations.

Transplantation-free survival

During a median follow-up of 4.3 years, 15 children died and 1 child underwent lung transplantation (Figure 3). The cause of death was directly PAH-related in 10 children and not directly PAH-related in the remaining 5 children, although the condition causing death might have been poorly tolerated because of the presence of PAH.

In group 1, 3 children died. Of interest, all three children were diagnosed with advanced PAH within six months after birth.

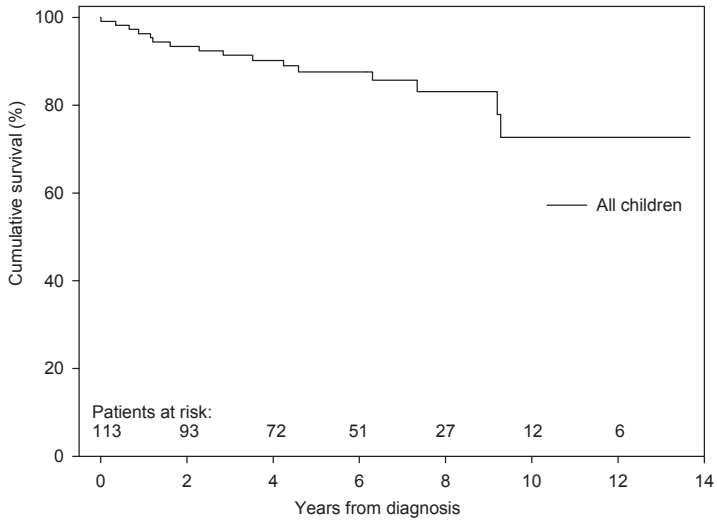

Figure 3. Transplantation-free survival of all children with pulmonary arterial hypertension associated with congenital heart disease
Survival at 1, 3, and 5 years was 96%, 91%, and 88%, respectively.

With the relatively low number of 16 events, an exploratory survival analysis could not demonstrate a significant survival difference between the four groups of the Nice-CHD-classification (Figure 4A). Also, despite the fact that all three deceased children with not-classifiable PAH-CHD died within 3 years after diagnosis, no survival differences could be observed between this group and the four groups of the Nice-CHD-classification (p=0.32). Finally, no survival differences between children with a hemodynamically relevant shunt-defect (groups 1 and 2 combined) and those without such a shunt-defect (groups 3 and 4 and not-classifiable PAH-CHD) could be demonstrated (Figure 4B).

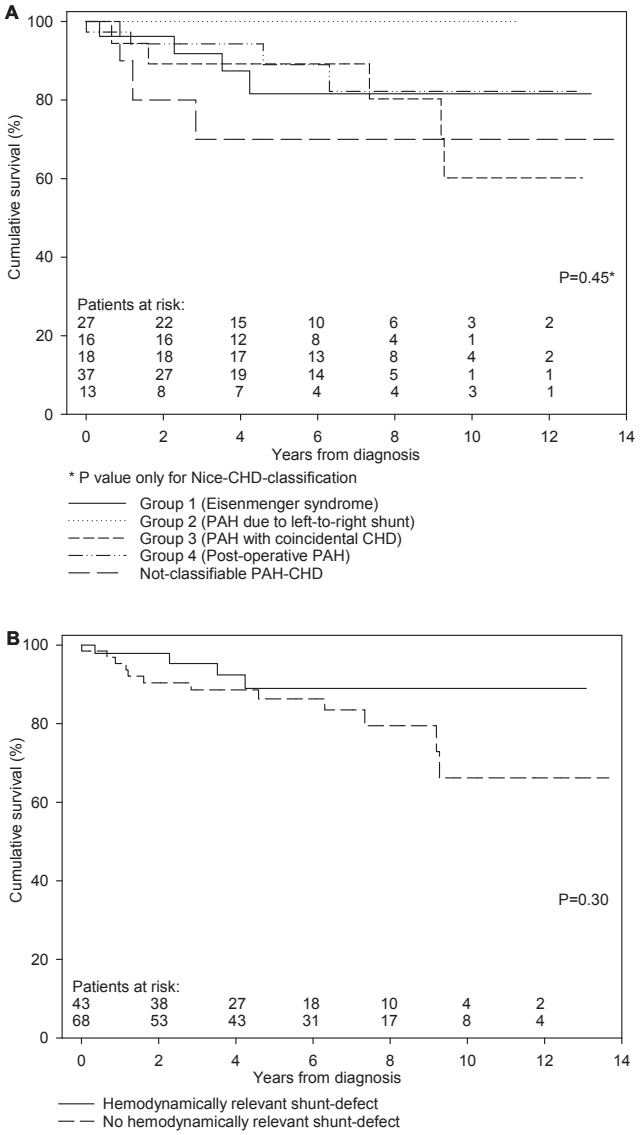

Figure 4. Transplantation-free survival stratified by the Nice-CHD-classification and the hemodynamic relevance of the shunt-defect

A. Stratified by the Nice-CHD-classification. Survival at 1, 3, and 5 years was 96%, 92%, and 82% for children in group 1, 100%, 100%, and 100% for children in group 2, 94%, 89%, and 89% for children in group 3, and 97%, 94%, and 89% for children in group 4, respectively (p=0.45). Also shown is survival for children with not-classifiable CHD, with 1-, 3- and 5-year survival of 90%, 70%, and 70%, respectively.

B. Stratified by the hemodynamic relevance of the shunt-defect. Survival at 1, 3, and 5 years was 98%, 95%, and 89% for children with a hemodynamically relevant shunt-defect (groups 1 and 2) and 95%, 89%, and 86% for children without a hemodynamically relevant shunt-defect (group 3 and 4 and not-classifiable CHD), respectively (p=0.30). CHD, congenital heart disease; PAH, pulmonary arterial hypertension.

DISCUSSION

This study is the first to assess the applicability and value of the recently proposed Nice-CHD-classification in children with PAH-CHD. In our study, this classification identified clinically relevant differences in patient and disease characteristics between groups, especially regarding comorbidities, hemodynamic profile, and treatment intensity. However, a substantial proportion of children (11%) could not be classified, as their CHD did not fit in the predefined groups, which are based on congenital shunt-defects. In this exploratory study with a relatively low event rate, no differences in transplantation-free survival between the four groups of the Nice-CHD-classification could be observed.

Nice-CHD-classification

ES, group 1, is the advanced stage of PAH associated with congenital shunt-defects, with reversed or bidirectional shunting and the occurrence of cyanosis. This condition is distinguished from shunt-defects with left-to-right shunting, group 2. However, this distinction is artificial, since a gradual progression of patients from the latter group to group 1 over time is to be expected (as we observed in 6 patients in this study), complicating group-specific outcome analyses. Furthermore, children in groups 1 and 2 had similar underlying CHD: predominantly post-tricuspid shunt-defects. Patients with ES had most advanced PAH, characterized by unfavorable pulmonary-to-systemic hemodynamics. However, cardiac index and mRAP seemed preserved in these children. This is likely to be associated with the hemodynamically relevant shunt-defect that may function as "pop-off" for the right ventricle, preserving left ventricular filling and cardiac output. Despite this, children in group 1 were in higher WHO-FC, which might be explained by the accompanying cyanosis that aggravates during exercise.[18]

Objective criteria are lacking for "coincidental CHD", in which the presence of a (small) shunt-defect itself is not considered to account for the development of PAH. In our study, this was addressed by independent review of the treating physician's assessment. Nevertheless, children in group 3 indeed seemed to form a distinct disease entity, with a preponderance of pre-tricuspid shunt-defects and no complex CHD. Although comorbidities are frequent in all forms of pediatric PAH-CHD, as shown in this and other studies[10,19,20], children in group 3 showed a different pattern of extracardiac comorbidities, characterized by lower frequency of Down syndrome and higher frequency of other (un)defined syndromes. These features are in line with those found in children with idiopathic PAH, justifying previous reports that classified this condition as "idiopathic-like PAH".[10] It seems that, in children, extracardiac comorbidities, such as undefined syndromes or certain genetic traits, are associated with the development of PAH. Increased genetic susceptibility for a normally non-pathogenic "hit" may be the mechanism, where in these group 3 children the small heart defect and normally non-relevant shunt may

form this second hit and initiate or accelerate the pulmonary vascular remodeling of PAH.

Remarkably, in this contemporary cohort, group 4 (postoperative PAH) was the largest group. This is in line with earlier data from the Spanish Registry for Pulmonary Hypertension and the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry.[20,21] Shunt closure in early stages of PVD can reverse and resolve PAH.[6] Therefore, it is generally advised to close shunt-defects early in life, usually within the first 1-2 years of life, depending on the defect, as was done in most of the children in this study. However, this study shows that early closure does not always prevent the development of progressive PAH. This is in line with epidemiological data on pediatric PAH showing that 1-2% of children with PAH-CHD developed PAH despite early closure of their shunt-defect.[7] Also, in our study extracardiac factors were frequent in the group with postoperative PAH: one-third had Down syndrome and 22% had other comorbidities. These factors may affect susceptibility for PVD and play a role in progression of PAH after shunt closure. Therefore, next to young age and hemodynamics, such factors should also be taken into account when determining eligibility for shunt closure.[4,6,22]

Therapy

Remarkably, although there is no evidence supporting the use of CCBs in PAH-CHD, 7 children without hemodynamically relevant shunt-defects received CCB monotherapy in this study.

Most children received PAH-targeted therapies, confirming previous current era reports.[9,23,24] Interestingly, children in group 3 received more intense PAH-targeted therapy than children in other groups, although they did not have more advanced disease based on WHO-FC or hemodynamic profile. This suggests that these children were considered more similar to patients with idiopathic PAH and different from the other children with PAH-CHD.

In the original cohort, we have shown that children with PAH-CHD were treated less intensely than children with idiopathic/hereditary PAH.[9,25] In the current study, about half of the children did not receive PAH-targeted dual or triple therapy. In the light of the unfavorable prognosis for these children, with a 3-year mortality rate of approximately 10%, it should be questioned whether this less intense treatment is justified and whether more intense treatment might improve survival in these children. Further research is required to answer these questions.

Survival

Overall 5-year survival in this study was 88%, which was within the range of previously reported survival rates in pediatric PAH-CHD.[7,20,24,26-29] In contrast to the recent report of Manes et al.[15] describing outcomes in adult PAH-CHD, we could not demonstrate

survival differences within the Nice-CHD-classification. The relatively low number of patients and endpoints and the relatively short follow-up time in this study, resulting in lack of power, hampered conclusions from the exploratory survival analysis in the current study.

In this study, ES was diagnosed in three infants within the first 6 months of life, and all died during follow-up. Rather than the classic disease evolution into ES, these infants probably had a failure of postnatal adaptation with remodeling of the pulmonary vascular bed. These observations are in line with the statement of the Pulmonary Vascular Research Institute (PVRI) task force that perinatal and in-utero factors affecting the pulmonary vascular bed are important in determining postnatal outcome.[30] This maladaptation may contribute to a rapid progression of PAH, and such infants presenting with "accelerated PAH" have been shown to have a very poor prognosis.[4,7,31] In fact, these children may represent a form of persistent pulmonary hypertension of the newborn with associated or coinciding with CHD.

None of the children in group 2 died or underwent lung transplantation. This could very well be due to the artificial distinction between group 1 and group 2, as children in group 2 will first progress into group 1 before they die or undergo lung transplantation.

In this study, survival of children in group 3 seemed better than that reported for children with idiopathic PAH.[27,32]Although not sufficient to explain the PAH, their shunt-defect may contribute to preservation of cardiac output despite progression of PVD.[15]

While children and adults in group 4 have been reported to have worse survival than children with other CHD, this could not be demonstrated in this study.[7,23] This may be due to patient selection and inclusion. Only children with PAH confirmed during cardiac catheterization at least 1 year after cardiac surgery were included in this study. Therefore, the sickest patients may not have been included, as they might have been too sick to undergo cardiac catheterization or died within the first year after cardiac surgery. Also, it may be that the worse survival of children with postoperative PAH occurs only after a longer period of follow-up.

It is important to notice that the inclusion criteria of this study were designed to study a contemporary cohort with predominantly incident patients but also allowed the inclusion of a small subset of prevalent patients (n=18). Prevalent patients were seen in the referral centers between 2000 and 2010 but had diagnostic cardiac catheterization between 1997 and 2000. To avoid immortal-time bias, data of these patients were left truncated. For patients with PAH after repaired CHD, the inclusion criteria required a diagnostic cardiac catheterization performed more than 1 year after corrective surgery. Children who died within 1 year after surgery were thus not included in this cohort. This might have introduced a limited form of immortal-time bias.

Not-classifiable CHD

The Nice-CHD-classification is based on the presence or history of shunt-defects. However, a significant number of children (13%) had CHD other than shunt-defects. Only two of these children, with major aortopulmonary collateral arteries, could be classified as group 5 PH according to the Nice classification, whereas the remaining children could not be classified. The heterogeneity of CHD associated with PH and the difficulties and limitations of simple classification have been repeatedly raised and are at odds with the advantages of stratification for risk or treatment effect that may be associated with such classification.[33] The Panama classification, as proposed by the PVRI task force, aims to address this heterogeneity in pediatric PAH but awaits validation with respect to its value for risk stratification, prognostication, or treatment consequences.[30] More research is needed to further characterize children with not-classifiable PAH-CHD.

Strengths and limitations

Bringing together the consecutive, contemporary cohorts of three major pediatric PAH referral centers has led to one of the largest contemporary cohorts in the field of pediatric PAH and provided the opportunity to assess the applicability of the Nice-CHD-classification in children. Nevertheless, this study was limited by the relatively low number of events, resulting in lack of power and thereby hampering definitive conclusions regarding survival. Also, its retrospective nature can be regarded a limitation. However, the standardized diagnostic and treatment strategies of three dedicated pediatric PH centers and a dedicated review at the level of individual patient data for this study allowed for a meticulous characterization of the patients and minimized differences in definitions or data inconsistencies. In our cohort, only children who had a diagnosis of PAH confirmed during cardiac catheterization were included, which strengthened disease definition but also introduced a selection bias by exclusion of children with PAH-CHD without cardiac catheterization. Furthermore, baseline was defined as the moment of diagnostic cardiac catheterization, which also strengthened disease definition but may have postponed time of diagnosis, affecting survival analyses.

Conclusions

Pediatric PAH-CHD is a heterogeneous condition frequently associated with extracardiac, syndromal and developmental factors that are believed to affect PAH evolution and progression. The recently proposed Nice-CHD-classification identifies groups with specific patient and disease characteristics, also in children. However, the fact that a substantial proportion of children with PAH-CHD, 11%, could not be classified within this classification forms a serious limitation. Group 3, PAH with coincidental CHD, forms a distinct disease entity similar to idiopathic PAH. The prognostic value of the Nice-CHD-classification in children with PAH-CHD could not be determined by this study because

of the relatively low number of events during a median follow-up of 4.3 years. The proposed Nice-CHD-classification supports clinical characterization of PAH-CHD; however, further refinement is needed in order to adequately classify all children with PAH-CHD.

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REFERENCES

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-1900.
2. Berman EB, Barst RJ. Eisenmenger's syndrome: Current management. Prog Cardiovasc Dis. 2002;45(2):129-138.
3. Tulloh RM. Congenital heart disease in relation to pulmonary hypertension in paediatric practice. Paediatr Respir Rev. 2005;6(3):174-180.
4. van Albada ME, Berger RM. Pulmonary arterial hypertension in congenital cardiac disease--the need for refinement of the evian-venice classification. Cardiol Young. 2008;18(1):10-17.
5. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. Circulation. 1968;37(5):805-815.
6. Rabinovitch M, Keane JF, Norwood WI, Castaneda AR, Reid L. Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects. Circulation. 1984;69(4):655-667.
7. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
8. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
9. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
10. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: Complex presentation and diagnosis. J Pediatr. 2009;155(2):176-82.e1.
11. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
12. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
13. Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. factors relating to deterioration and death. Eur Heart J. 1998;19(12):1845-1855.
14. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in eisenmenger syndrome: A combined retrospective and case-control study. Eur Heart J. 2006;27(14):1737-1742.
15. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: A comparison between clinical subgroups. Eur Heart J. 2014;35(11):716-724.
16. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. Cardiovasc Res. 1970;4(1):23-30.
17. Bergstra A, van Dijk RB, Hillege HL, Lie KI, Mook GA. Assumed oxygen consumption based on calculation from dye dilution cardiac output: An improved formula. Eur Heart J. 1995;16(5):698-703.
18. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. Circulation. 2005;112(6):828-835.

19. Levy M, Celermajer D, Szezepanski I, Boudjemline Y, Bonnet D. Do tertiary paediatric hospitals deal with the same spectrum of paediatric pulmonary hypertension as multicentre registries? Eur Respir J. 2013;41(1):236-239.
20. del Cerro Marin MJ, Sabate Rotes A, Rodriguez Ogando A, et al. Assessing pulmonary hypertensive vascular disease in childhood. data from the spanish registry. Am J Respir Crit Care Med. 2014;190(12):1421-1429.
21. Beghetti M, Schulze-Neick I, Barst RJ, Kronmal D, Berger RMF, Humpl T. Clinical classification of congenital heart disease associated pulmonary hypertension. does it work for pediatrics? analysis of the TOPP registry (tracking outcome and practice in pediatric pulmonary hypertension). Cardiology in the Young. 2012;22(Supplement S1):S3-S176.
22. Lopes AA, Barst RJ, Haworth SG, et al. Repair of congenital heart disease with associated pulmonary hypertension in children: What are the minimal investigative procedures? consensus statement from the congenital heart disease and pediatric task forces, pulmonary vascular research institute (PVRI). Pulm Circ. 2014;4(2):330-341.
23. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
24. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
25. Zijlstra WMH, Douwes JM, Rosenzweig EB, et al. Children with pulmonary arterial hypertension (PAH) associated with congenital heart disease are treated less intensively with PAH-targeted drugs compared to children with idiopathic/hereditary PAH. Eur Heart J. 2013;34(Suppl 1):Suppl 1.
26. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL registry). Am J Cardiol. 2014;113(1):147-155.
27. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
28. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: Occurrence and prognostic value when comparing three response criteria. Eur Heart J. 2011;32(24):3137-3146.
29. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
30. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI pediatric taskforce, panama 2011. Pulm Circ. 2011;1(2):286-298.
31. van Loon RL, Roofthooft MT, Berger RM. Pulmonary arterial hypertension in children with congenital heart disease. PVRI review. 2009;1(4):203-207.
32. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
33. Berger RM. Pulmonary hypertension: Smaller kids, smaller steps. Lancet Respir Med. 2014;2(5):348-350.

3

Pulmonary arterial hypertension in children after neonatal arterial switch operation

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ABSTRACT

Background– Pediatric pulmonary arterial hypertension (PAH) after neonatal arterial switch operation (ASO) for transposition of the great arteries (TGA) is a clinically recognized entity with an estimated incidence of 0.6-1.0%. Nevertheless, a clinical characterization is lacking. We present an international cohort of children with PAH after neonatal ASO for TGA and describe epidemiology and clinical course.

Methods– Data were collected of children with PAH after neonatal ASO (≤6 weeks after birth) for simple TGA without residual shunt-defects, identified in four national pediatric PAH-networks in Europe and one US-referral center.

Results– Twenty-five children were identified between 1989 and 2014. In 17 children (68%), PAH was detected <1 year after ASO. In the remaining children PAH was detected after median 64 months (IQR 24.5, 94.5). Twenty-four children (96%) received PAH-targeted therapies. During follow-up after ASO (median 5.2 years), 8 children died, 4 underwent lung-transplantation and 2 received a Potts shunt. One- and 5-year Potts shunt- and transplant-free survival after ASO was 100% and 73%. From first PAH-detection this was 100% and 58%, respectively, which did not differ between children with early (<1 year after ASO) or late PAH-detection.

Conclusions– The occurrence of PAH after ASO for TGA represents a specific association. PAH-onset may be early or late after ASO, with similar fatal course from first PAH-detection. Mechanisms leading to PAH in this association are unknown, but may include abnormal prenatal pulmonary hemodynamics and/or genetic susceptibility. Routine, lifelong follow-up for children who undergo ASO for TGA should include screening for PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and progressive disease of the pulmonary vasculature and has a poor prognosis.[1] In children, PAH has an estimated annual incidence rate of approximately 3 cases per million children and is most frequently idiopathic or associated with congenital heart disease (CHD).[1,2] CHD in PAH typically includes the presence or history of a shunt-defect, as increased pulmonary blood flow is believed to trigger the remodelling of small pulmonary arteries that is characteristic for PAH.[3] However, PAH has also been reported in children with CHD other than shunt-defects.[2,4]

Transposition of the great arteries (TGA) is one of the most common cyanotic CHD, contributing to approximately 5% of all CHD.[5] Early development of severe pulmonary vascular disease (PVD) has been well recognized in patients with uncorrected TGA.[6,7] With its occurrence reported already in the first weeks of life, PVD in TGA seems to develop more rapidly than in other types of CHD.[7,8]

In earlier days, surgical management for TGA consisted of functional repair with an atrial redirection procedure (the Mustard or Senning procedure). These procedures were usually performed in the second half of the first year of life or even later, resulting in long-term presence of cyanosis and shunt-lesions. Consequently, PAH is a well-recognized late complication of these procedures and has been reported to occur in approximately 7% of patients who survive into adulthood.[9]

Since the 1980s the arterial switch operation (ASO) has become the treatment of choice for simple TGA.[10] This procedure, in which the pulmonary artery and aorta are literally switched and the coronary arteries reimplanted, provides an anatomical repair and has a very good prognosis.[11] The operation is usually performed within the first 2 weeks of life, precluding the presence of a long-term shunt-lesion as a trigger for the development of PAH in patients with TGA.

Nevertheless, the association of PAH and TGA, also after a successful neonatal ASO, has been clinically recognized in pediatric pulmonary hypertension (PH) centers. An explanation for this association is unknown, but proposed mechanisms include programming of endothelial dysfunction due to prenatal hypoxic or postnatal hyperoxic blood perfusing the pulmonary vasculature in uncorrected TGA, genetic susceptibility, abnormal bronchial circulation and the dispersion of microthrombi, for instance during atrial balloon septostomy.[12-14]

To date, however, a clinical characterization of presentation, risk factors and prognosis of this entity is lacking. With the current study, we aim to characterize this clinical entity by presenting an international cohort of children with PAH after neonatal ASO for TGA and describing its epidemiology and clinical course.

METHODS

This study is a retrospective, international multicenter study. Children with PAH and TGA repaired in the neonatal period with ASO between 1989 and 2014 were identified from nine dedicated pediatric PH centers in Europe and the United States, including four national registries (United Kingdom, France, Spain and the Netherlands). Ethical approval for the registries was obtained from the institutional review boards (of the constituent/participating registries) and the participants or their guardians provided written informed consent at enrolment.

Neonatal correction was defined as ASO within six weeks after birth. To exclude PAH associated with shunt-defects, only patients with no hemodynamically relevant residual shunt-defects after ASO were included in this study.

Patients and data collection

Patient characteristics were collected from patient charts including gestational age, sex, medical history, the presence of other possible PAH associated conditions and anatomical cardiac diagnosis. Only children with no hemodynamically relevant residual lesions were included, thus only patients with isolated TGA or TGA associated with a ventricular septal defect (VSD) that had been successfully closed during ASO. Also, children with residual pulmonary branch stenosis or impaired left ventricular function were not included in this study. Parameters regarding the ASO and post-operative phase included whether there were any PAH-relevant complications and/or pulmonary hypertensive crises peri-ASO.

PAH was confirmed by cardiac catheterization in all but 1 patient. PAH was defined as a mean pulmonary artery pressure ≥25 mmHg with a mean pulmonary capillary wedge pressure ≤15 mmHg. In one child mean pulmonary capillary wedge pressure was not available at cardiac catheterization and another child had an echocardiographic PAH diagnosis. In both children left heart disease was excluded by echocardiography on review of the center's expert physician. The age of first PAH detection, either with echocardiography or cardiac catheterization, was determined.

Treatment information included the use of supportive therapies, PAH-targeted therapies (including endothelin receptor antagonists, type 5 phosphodiesterase inhibitors and prostanoids) and surgical interventions during follow-up, i.e. atrial balloon septostomy, Potts shunt or lung transplantation. Treatment intensity was defined as the number of PAH-targeted drugs at endpoint or last follow-up (PAH-targeted mono-, dual or triple therapy).

Statistics

Data are presented as number (percentage) or median (interquartile range) when appropriate. The first occurrence of Potts shunt, lung transplantation or death was defined as the primary endpoint in this study. Patients who did not die nor received a Potts shunt nor underwent lung transplantation were censored at the last follow-up visit. Potts shunt- and transplant-free survival was depicted using Kaplan-Meier curves. Differences in survival were explored using the log-rank test. P-values <0.05 were considered significant.

RESULTS

Patients

In total, 25 children with PAH and neonatal ASO for TGA were identified (Table 1). All children were born after a gestational age of at least 36 weeks. Most children (76%) were males. Nineteen children (76%) had an intact ventricular septum and six had a concomitant VSD (Table 2). Four children (17%) had a history of perinatal asphyxia. Three (13%) had associated persistent pulmonary hypertension of the newborn (PPHN). One of whom required peri-operative extracorporeal membrane oxygenation. No recognized comorbidities, syndromes or dysmorphic features were reported, except for epilepsy and hydrocephalus associated with perinatal asphyxia in one child. No other causes for or conditions associated with PAH were identified in any of the children

Table 1. Participating networks/centers and number of patients

Continent	Network / Center	Number of patients
Europe	The National Paediatric Pulmonary Hypertension Service United Kingdom Great Ormond Street Hospital for Children, London, United Kingdom	9
	French Pediatric Pulmonary Hypertension registry Necker Hospital for Sick Children, Paris, France	5
	The Dutch National Referral Center for Pulmonary Hypertension in Childhood Beatrix Children's Hospital, University Medical Center Groningen, the Netherlands	3
	The Spanish registry for Pediatric Pulmonary Hypertension (REHIPED)	
	University Hospital Ramon y Cajal, Madrid, Spain	1
	University Hospital Doce de Octubre, Madrid, Spain	2
	University Hospital Virgen del Rocio, Seville, Spain	1
	University Hospital Vall d'Hebrón, Barcelona, Spain	2
United States	Children's Hospital Colorado, Aurora, Colorado	2

Table 2. Patient characteristics and ASO

	All patients (n=25)
	Value
Male	19 (76)
Anatomic diagnosis	
TGA-IVS	19 (76)
TGA with VSD	6 (24)
Perinatal asphyxia*	4 (17)
PPHN*	3 (13)
Atrial balloon septostomy	21 (84)
Age atrial balloon septostomy (days)	1 (1, 1)
Age ASO (days)	8 (6, 10)
PH crisis peri-ASO	2 (8)
Successful ASO	25 (100)
Hemodynamically relevant residual lesions	0
Other causes for PAH	0

Data presented as number (percentage) or median (interquartile range). *, missing in 1 child. ASO, arterial switch operation; IVS, intact ventricular septum; P(A)H, pulmonary (arterial) hypertension; PPHN, persistent pulmonary hypertension of the newborn; TGA, transposition of the great arteries; VSD, ventricular septum defect.

Twenty-one children (84%) underwent an atrial balloon septostomy in the first days of life. Median age of ASO was 8 days. Four children had a small (residual) VSD after ASO, considered not hemodynamically relevant.

At first cardiac catheterization post-ASO median mean pulmonary artery pressure was 48 mmHg and median indexed pulmonary vascular resistance was 11.5 Wood units.m^2 (Table 3).

Time of PAH detection

Median age at first PAH detection was 3 months (IQR 1, 14) with a range of 1 to 137 months (Table 3). In fact, PAH was detected within one year after ASO in 17 children (68%) with a median age at first PAH detection of 1.5 months (IQR 1, 3). In the remaining 8 children median age at first PAH detection was 64 months (IQR 19.5, 94.5). Patient and disease characteristics, as shown in Tables 2 and 3, did not differ between these two groups. All three children with PPHN had first PAH detection within one year after ASO.

Table 3. PAH characteristics

	All patients (n=25)	
	N	Value
Age first PAH detection (months)	25	3 (1, 14)
PAH detection within one year after ASO	25	17 (68)
Age first detection (months)		1.5 (1, 3)
PAH detection more than one year after ASO	25	8 (32)
Age first detection (months)		64 (19.5, 94.5)
Age first RHC (months)	24	10 (2, 30)
mPAP (mmHg)	24	48 (37, 55)
mSAP (mmHg)	20	62 (51, 65)
mPAP/mSAP	20	0.82 (0.71, 1.07)
mPCWP (mmHg)	24	10 (8, 12)
PVRi (WU.m^2)	17	11.5 (8.7, 13.0)
PAH therapy	25	
CCB monotherapy		1 (4)
PAH-targeted mono therapy		6 (24)
PAH-targeted dual therapy		8 (32)
PAH-targeted triple therapy		10 (40)

Data presented as number (percentage) or as median (interquartile range). ASO, arterial switch operation; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; mSAP, mean systemic artery pressure; mPAP/mSAP, ratio between mean pulmonary and systemic artery pressure; PAH, pulmonary arterial hypertension; PVRi, indexed pulmonary vascular resistance; RHC, right heart catheterization; TGA, transposition of the great arteries; WU, Wood units.

Follow-up

Median follow-up after ASO was 5.1 years (IQR 2.9, 12.1). During follow-up, two children received a Potts shunt, four children underwent lung transplantation and eight children died. Of the eight deceased children, five died of progressive right ventricular failure, one of massive hemoptysis and two died during a follow-up cardiac catheterization, one of whom during atrial balloon septostomy procedure for PAH. One-, 3-, 5- and 10-year Potts shunt- and transplant-free survival rates after ASO were 100%, 82%, 73% and 65%, respectively (Figure 1). From first PAH detection these were 100%, 73%, 58% and 50%, respectively.

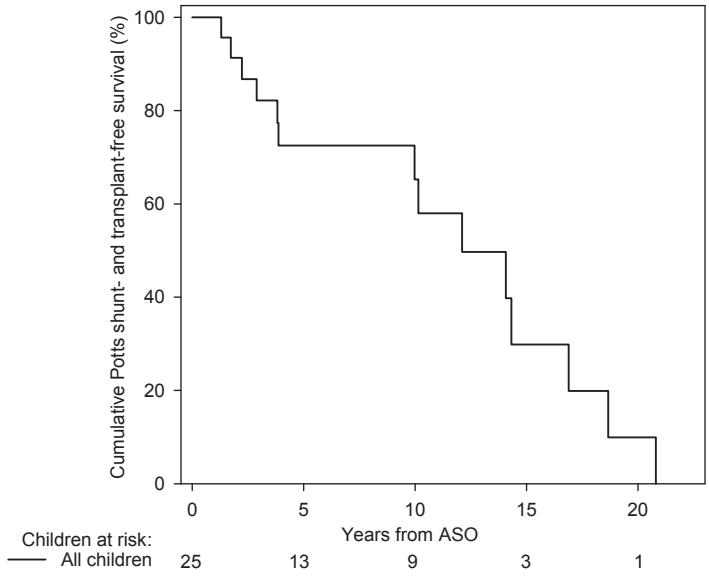

Figure 1. Potts shunt- and transplant-free survival from ASO of children with PAH after neonatal ASO for TGA

One-, 3-, 5-and 10-year survival after ASO was 100%, 82%, 73% and 65%, respectively.

ASO, arterial switch operation; PAH, pulmonary arterial hypertension; TGA, transposition of the great arteries.

Potts- and transplant-free survival from ASO of children with first PAH detection within one year after ASO was worse than survival of those with first PAH detection more than one year after ASO (p=0.039, Figure 2A). However, survival from first PAH detection did not differ between these two groups (p=0.409, Figure 2B).

During follow-up, four children underwent atrial balloon septostomy for treatment of PAH. Fourteen children (50%) received supportive therapies, including anticoagulation, diuretics and/or oxygen treatment. One child was on calcium channel blocker monotherapy after the parents had refused intravenous epoprostenol therapy, while other PAH-targeted therapy was not available at that time. Six children (24%) received PAH-targeted mono-, 8 (32%) dual and 10 (40%) triple therapy (Table 3).

Of the 11 children that did not die, neither underwent lung transplantation nor received a Potts shunt during follow-up, three children were in World Health Organization functional class (WHO-FC) I, 7 in WHO-FC II and one in WHO-FC III at last follow-up (median time from first PAH detection 4.4 years [IQR 1.8, 5.1]).

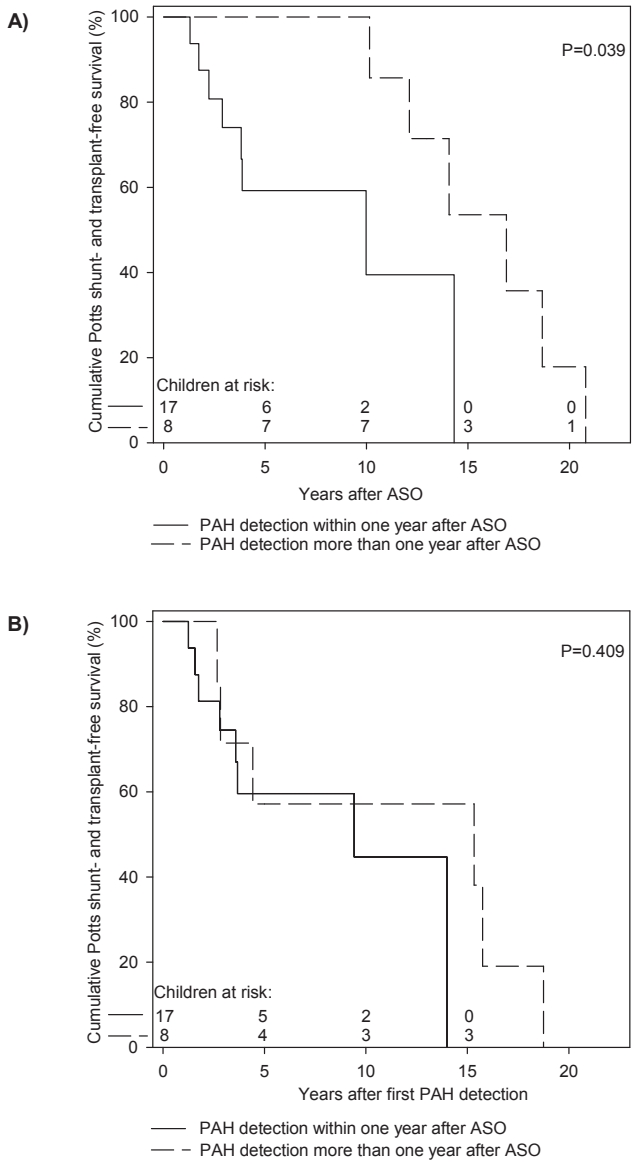

Figure 2. Potts shunt- and transplant-free survival of children with first PAH detection within and more than one year after ASO

A. Survival from ASO. One-, 3-, 5- and 10-year survival was 100%, 74%, 59% and 40% for the 18 children with first PAH detection within one year after ASO and 100%, 100%, 100% and 100% for the 7 children with first PAH detection more than one year after ASO, respectively (p=0.039).

B. Survival from first PAH detection. One-, 3-, 5-and 10-year survival was 100%, 75%, 60% and 45% for the 18 children with first PAH detection within one year after ASO and 100%, 71%, 57% and 57% for the 7 children with first PAH detection more than one year after ASO, respectively (p=0.409).

ASO, arterial switch operation; PAH, pulmonary arterial hypertension; TGA, transposition of the great arteries.

DISCUSSION

The current study describes a cohort of 25 children with a specific association: children with TGA that developed severe, progressive PAH after timely and successful ASO and in the absence of hemodynamically relevant residual lesions. PAH could present already very early after ASO, but also late, after several years. Despite the intense use of PAH-targeted therapies, Potts shunt- and transplant-free survival in this cohort was poor with a 5-year survival rate of 73% after ASO and 58% after first PAH detection. In these children, in whom ASO was performed at a median age of 8 days, there was no long-term shunting as trigger for the development of PAH. Therefore, these patients challenge the general concept of PAH associated with CHD, in which prolonged exposure to increased pulmonary blood flow due to a shunt-defect is considered the trigger for the development of advanced and irreversible pulmonary vascular remodelling.

Incidence of PAH after neonatal ASO for TGA

For this study, the total number of ASOs for TGA performed at each participating center or within each national cohort during the study period was not available. Therefore, the design of this study precluded the determination of an incidence rate of the association of PAH after successful neonatal ASO for TGA. After conscientiously studying the literature regarding PAH and ASO for TGA, we identified cases of PAH during follow-up in cohorts of children that underwent neonatal ASO for TGA. Out of 100 ASO procedures, Rivenes et al. described one child who underwent ASO at age 4 days and developed PAH at the age of 42 months.[15] In a series of 156 patients, Losay et al. mention one patient with PAH after ASO at the age of 2 weeks.[16] Cordina et al. describe a patient who underwent ASO for simple TGA in the neonatal period and presented with PAH at the age of 16 years.[17] Since the latter study included only patients ≥17 years of age, it was not included in incidence estimation. Finally, Roofthooft et al. identified one patient with PAH (included in the current study) from a consecutive series of 112 ASO-patients.[18] From these data, it can be roughly estimated that PAH after neonatal ASO for TGA may occur in 0.6-1.0% of the cases. This estimated incidence, based on literature review, precludes a merely coincidental concurrent occurrence of idiopathic PAH and TGA. The true incidence of the concurrence of TGA and PAH may be even higher since no systematic screening program for PAH after ASO has been reported and consequently patients with PAH might have been missed. Furthermore, prenatal or early severe PVD may cause children with TGA to die even before they undergo ASO.[19]

Clinical characterization

The male predominance observed in this cohort is in contrast to the generally observed female predominance in pediatric PAH.[2] This can be explained by the reported overall male predominance in TGA.[20]

In this cohort, we identified children with early-onset PAH, e.g. first PAH detection within one year after ASO, and children with late-onset PAH who had first PAH detection several years after ASO. Survival from ASO was better in this latter group, intrinsically associated with its definition. The observation that survival from first PAH detection did not differ between both groups implies that the PAH in the late-onset group actually developed later in life than in the early-onset group, instead of simply being detected later. Therefore, early- and late-onset PAH may represent two different phenotypes and we hypothesize that both phenotypes may be part of the spectrum of PVD associated with abnormal prenatal hemodynamics in TGA. We were not able to identify discriminating clinical characteristics in the early- or late-onset patients.

In the current clinical classification for PH, Nice, 2013, PAH associated with CHD is classified based on shunt status.[21] Since neonatal ASO for TGA precludes the presence of long-term postnatal shunting, such classification is not suitable. It has been previously advocated that pediatric PVD has specific aspects that are not sufficiently covered in the current classification for PH, including insults on developing and growing organs.[3,22,23] The clinical entity described in this manuscript illustrates the need for further "pediatric adaptations" of the current classification, with special attention for CHD other than shunt lesions and for the concept of programming due to pre- or postnatal abnormal conditions.

After first PAH detection, prognosis was poor and comparable to that of children with idiopathic PAH in the current era.[4] This is in sharp contrast to the excellent long term survival after ASO reported to be around 98% after 15 years, with approximately 80% freedom from reintervention.[11] Thus, this study shows that the occurrence of PAH early or late after ASO represents an important prognostic factor that significantly worsens prognosis. Therefore, the authors advocate that routine lifelong follow-up for children who undergo ASO for TGA should include screening for PAH to allow for early treatment initiation.

Although the proportion of children receiving PAH-targeted dual and especially triple therapy in this study is relatively high compared to what has been previously reported[4], a more aggressive and goal-oriented treatment strategy with early use of PAH-targeted combination therapy, as has been suggested for idiopathic PAH, seems to be justified also in these children.[24]

Underlying mechanisms

Alterations in prenatal pulmonary hemodynamics have been reported in foetuses with TGA including restriction or closure of the foramen ovale or ductus arteriosus. It has been suggested that such foetal alterations are associated with altered prenatal flow- and mixing-patterns resulting in hypoxia of the prenatal pulmonary circulation and increased bronchial circulation.[14,25,26] These alterations may contribute to the development of PVD, already prenatally, in foetuses with TGA. These foetuses are then at risk for rapid postnatal deterioration and death and also for developing postnatal PH.[14,19,25,26] These prenatal hemodynamic alterations may injure or program the developing pulmonary vasculature leading to abnormal postnatal responses. For the current study, foetal echocardiography data were not available. However, 84% of included children underwent an atrial balloon septostomy procedure in the first days of life. This proportion contrasts with the reported incidence of approximately 40% atrial balloon septostomy procedures in infants with TGA[27], suggesting that incomplete mixing and prenatal hemodynamic changes were more prevalent in these children. Also, the occurrence of PPHN, a condition of disturbed adaptation of the pulmonary vasculature to post-natal life, is more frequent in children with TGA than in the normal population, supporting this concept of altered prenatal pulmonary hemodynamics. PPHN has been suggested to be associated with abnormal pulmonary vascular responses and the development of PAH later in life.[2,28] In the current study, three children (13%) had PPHN. In a series described by Roofthooft et al., 14 of 112 infants with TGA presented with PPHN, of which 4 died preoperatively. One of the 10 children with PPHN that did undergo ASO developed PAH during follow-up (10%).[18] We hypothesize that the abnormal prenatal hemodynamics in TGA program the pulmonary vasculature leading to a spectrum of PVD including PPHN and PAH that may develop early (pre- or perinatally) or later in life.

Another potential explanation could be that a specific genetic make-up in patients with TGA predisposes for the development of PAH. Known PAH-related genes, such as bone morphogenetic protein type II receptor, have been explored for mutations in patients with PAH associated with CHD, but so far no such mutations have been shown in TGA.[29] However, very recently several candidate genes for TGA were identified.[30] Two of these genes, ACKR3 (or CXCR7) and NF1, have also been associated with endothelial dysfunction, pulmonary vascular remodelling and the development of PVD/PH.[31,32]

Strengths and limitations

This study is the first to characterize occurrence, presentation and clinical course of PAH in children after neonatal ASO for TGA. As such, this study identifies this specific clinical entity and provides clinically relevant information regarding its clinical features. The data are derived from 9 large pediatric cardiology centers, including 4 European national registries, enhancing epidemiologic strength and data quality.

The retrospective nature of the study is associated with inherent limitations. Patients with PAH after ASO might have been missed.. Data regarding the total number of ASOs performed in the participating centers or national cohorts during the study period were not available precluding the determination of an incidence rate of PAH after neonatal ASO for TGA from this study. Also, we could not compare children who developed PAH with children who did not, precluding the identification of risk factors for the development of PAH after neonatal ASO for TGA. In the current study perinatal asphyxia was described in 17% of the children and might have played a confounding role in the observed association of PAH and neonatal ASO for TGA. The current study does not allow to identify underlying mechanisms for the development of PAH in patients with TGA after ASO, and consequently, we can only speculate in this regard and provide supportive clinical data. Further research is needed to confirm the hypotheses regarding abnormal prenatal hemodynamics and genetic susceptibility.

Conclusions

Although PAH after successful neonatal ASO for TGA has been clinically recognized as a specific disease entity, the current study is the first to clinically characterize this association. In this cohort, two phenotypes could be distinguished: early-onset PAH, presenting weeks to months after ASO, and late-onset PAH, presenting years after ASO. In both phenotypes, prognosis is poor, despite the intense use of PAH-targeted therapies, and comparable to pediatric idiopathic PAH. This observational study did not allow for the identification of risk factors for the development of PAH after ASO for TGA. We speculate on the role of altered prenatal pulmonary hemodynamics in TGA, including abnormal flow- and mixing-patterns associated with prenatal presence of restrictive foramen ovale and ductus arteriosus, and of genetic susceptibility in these children. The data from the current study imply that routine, lifelong follow-up of children who underwent ASO for TGA should include screening for PAH in order to allow for early treatment initiation.

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REFERENCES

1. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
2. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
3. van Albada ME, Berger RM. Pulmonary arterial hypertension in congenital cardiac disease--the need for refinement of the evian-venice classification. Cardiol Young. 2008;18(1):10-17.
4. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
5. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241-2247.
6. Kumar A, Taylor GP, Sandor GG, Patterson MW. Pulmonary vascular disease in neonates with transposition of the great arteries and intact ventricular septum. Br Heart J. 1993;69(5):442-445.
7. Haworth SG. Pulmonary vascular disease in different types of congenital heart disease. implications for interpretation of lung biopsy findings in early childhood. Br Heart J. 1984;52(5):557-571.
8. Viles PH, Ongley PA, Titus JL. The spectrum of pulmonary vascular disease in transposition of the great arteries. Circulation. 1969;40(1):31-41.
9. Ebenroth ES, Hurwitz RA, Cordes TM. Late onset of pulmonary hypertension after successful mustard surgery for d-transposition of the great arteries. Am J Cardiol. 2000;85(1):127-30, A10.
10. Jatene AD, Fontes VF, Souza LC, Paulista PP, Neto CA, Sousa JE. Anatomic correction of transposition of the great arteries. J Thorac Cardiovasc Surg. 1982;83(1):20-26.
11. Shim MS, Jun TG, Yang JH, et al. Current expectations of the arterial switch operation in a small volume center: A 20-year, single-center experience. J Cardiothorac Surg. 2016;11(1):34-016-0428-9.
12. Newfeld EA, Paul MH, Muster AJ, Idriss FS. Pulmonary vascular disease in transposition of the great vessels and intact ventricular septum. Circulation. 1979;59(3):525-530.
13. Wernovsky G, Bridges ND, Mandell VS, Castaneda AR, Perry SB. Enlarged bronchial arteries after early repair of transposition of the great arteries. J Am Coll Cardiol. 1993;21(2):465-470.
14. Rudolph AM. Aortopulmonary transposition in the fetus: Speculation on pathophysiology and therapy. Pediatr Res. 2007;61(3):375-380.
15. Rivenes SM, Grifka RG, Feltes TF. Development of advanced pulmonary vascular disease in D-transposition of the great arteries after the neonatal arterial switch operation. Tex Heart Inst J. 1998;25(3):201-205.
16. Losay J, Planche C, Gerardin B, Lacour-Gayet F, Bruniaux J, Kachaner J. Midterm surgical results of arterial switch operation for transposition of the great arteries with intact septum. Circulation. 1990;82(5 Suppl):IV146-50.
17. Cordina R, Celermajer D. Late-onset pulmonary arterial hypertension after a successful atrial or arterial switch procedure for transposition of the great arteries. Pediatr Cardiol. 2010;31(2):238-241.
18. Roofthooft MT, Bergman KA, Waterbolk TW, Ebels T, Bartelds B, Berger RM. Persistent pulmonary hypertension of the newborn with transposition of the great arteries. Ann Thorac Surg. 2007;83(4):1446-1450.

19. Soongswang J, Adatia I, Newman C, Smallhorn JF, Williams WG, Freedom RM. Mortality in potential arterial switch candidates with transposition of the great arteries. J Am Coll Cardiol. 1998;32(3):753-757.
20. Egbe A, Uppu S, Stroustrup A, Lee S, Ho D, Srivastava S. Incidences and sociodemographics of specific congenital heart diseases in the united states of america: An evaluation of hospital discharge diagnoses. Pediatr Cardiol. 2014;35(6):975-982.
21. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
22. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI pediatric taskforce, panama 2011. Pulm Circ. 2011;1(2):286-298.
23. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: Complex presentation and diagnosis. J Pediatr. 2009;155(2):176-82.e1.
24. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
25. Maeno YV, Kamenir SA, Sinclair B, van der Velde ME, Smallhorn JF, Hornberger LK. Prenatal features of ductus arteriosus constriction and restrictive foramen ovale in d-transposition of the great arteries. Circulation. 1999;99(9):1209-1214.
26. Porayette P, van Amerom JF, Yoo SJ, Jaeggi E, Macgowan CK, Seed M. MRI shows limited mixing between systemic and pulmonary circulations in foetal transposition of the great arteries: A potential cause of in utero pulmonary vascular disease. Cardiol Young. 2015;25(4):737-744.
27. Ruys TP, van der Bosch AE, Cuypers JA, et al. Long-term outcome and quality of life after arterial switch operation: A prospective study with a historical comparison. Congenit Heart Dis. 2013;8(3):203-210.
28. Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. Augmented vasoreactivity in adult life associated with perinatal vascular insult. Lancet. 1999;353(9171):2205-2207.
29. Roberts KE, McElroy JJ, Wong WP, et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J. 2004;24(3):371-374.
30. Costain G, Lionel AC, Ogura L, et al. Genome-wide rare copy number variations contribute to genetic risk for transposition of the great arteries. Int J Cardiol. 2016;204:115-121.
31. Costello CM, McCullagh B, Howell K, et al. A role for the CXCL12 receptor, CXCR7, in the pathogenesis of human pulmonary vascular disease. Eur Respir J. 2012;39(6):1415-1424.
32. Montani D, Coulet F, Girerd B, et al. Pulmonary hypertension in patients with neurofibromatosis type I. Medicine (Baltimore). 2011;90(3):201-211.

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Current and advancing treatments for pulmonary arterial hypertension in childhood

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe and progressive intrinsic disease of the precapillary lung vasculature. Since the introduction of PAH-targeted drugs, survival of PAH patients seems to have improved. Randomized controlled trials have led to evidence-based guidelines to direct treatment in adults. However, since disease characteristics differ between adults and children, it is hazardous to simply extrapolate these guidelines to children. Moreover, pediatric data on treatment strategies and how to assess treatment response remain virtually absent. Optimal treatment strategies are highly needed to guide therapy and improve survival in children with PAH. This review provides an overview of currently available treatments of PAH and the limited efficacy and safety data in children (with the exclusion of perinatal pulmonary vascular diseases, as persistent pulmonary hypertension of the newborn). We also discuss potential treatment goals and how the available data can be translated into treatment strategies in pediatric PAH.

INTRODUCTION

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg.[1] PH can be classified into five subgroups, with PH group 1 being pulmonary arterial hypertension (PAH). In contrast to the other four subgroups of PH, PAH is a progressive intrinsic disease of the precapillary pulmonary vessels characterized by unique vascular neointimal lesions.[2] These result in elevation of the mPAP and pulmonary vascular resistance (PVR) leading to right-sided heart failure and ultimately death. PAH has a poor prognosis with a median survival of 2.8 years in untreated adults.[3] Survival in children is believed to be even worse. Also, PAH is a rare disease, with estimated prevalence rates ranging from 6.6 to 26 cases per million adults and 20 cases per million children.[4-6] In children, estimated incidence rates for idiopathic PAH (IPAH) are 0.48 to 0.7 cases per million children per year.[6,7]

Although the pathophysiology of PAH is not completely understood, it is believed that endothelial dysfunction is a key component.[2,8] Endothelial dysfunction is associated with a decreased production of vasodilators with antiproliferative properties and an increased production of vasoconstrictors with proliferative properties. This leads to an increased pulmonary vascular muscle tone and to proliferation of vascular smooth muscle and endothelial cells. In the past decades, three major pathways have been identified in this process.[9] The prostacyclin and nitric oxide (NO) pathways both lead to vasodilatation and antiproliferation. The endothelin-1 pathway has opposite effects and leads to vasoconstriction and proliferation. Three major classes of drugs interfering with these pathways have been developed: prostanoids, substituting prostacyclin, phosphodiesterase-5 (PDE-5) inhibitors, promoting the effects of NO and endothelin receptor antagonists (ERAs), inhibiting the effects of endothelin-1.

Very recently, novel drugs that interfere at different points in these pathways have either been approved or are in the stage of a Phase III clinical trial. These include the soluble guanylate cyclase stimulator riociguat that targets the NO pathway and the oral prostacyclin receptor antagonist selexipag.[10,11]

Based on multiple randomized controlled trials (RCTs) in adult PAH patients, evidence-based treatment guidelines have been developed and survival seems to have improved since the introduction of PAH-targeted drugs.[1,12,13] Although there are similarities between adult and pediatric PAH, important differences in pathophysiology, underlying conditions, clinical presentation and outcome exist so that adult treatment algorithms cannot simply be extrapolated to children.[14-16] For instance, in around 50% of children, PAH is associated with congenital heart defects that are often more complex than those in adults. PAH associated with connective tissue disease, portal hypertension or drugs is rare in children.[6,17-20] Furthermore, in IPAH, syncope occurs more often in children, while heart failure is more frequent in adults.[15] However, to date, there are no specific

guidelines for the treatment of pediatric PAH and its development is hampered by the lack of RCTs in children. Although available data on the treatment of pediatric PAH are accumulating, this predominantly includes observational data based on single-center studies, small select patient groups or registries. These have provided safety and tolerability data, but no controlled data on efficacy. The available pediatric data suggest that survival has also improved in children since the introduction of the PAH-targeted drugs.[18,21-25] However, survival remains unsatisfactory (Figure 1) with 5-year survival rates ranging from 71 to 81%, illustrating the high unmet need for treatment guidelines specifically for the pediatric age group.[18,21-25] Optimal treatment strategies, including adequate monitoring of treatment response, are essential to guide therapy and may improve survival in children with PAH.

This review will provide an overview of the currently available treatments for PAH and the limited data on efficacy and safety in children with PAH (with the exclusion of perinatal pulmonary vascular diseases, such as persistent PH of the newborn). Furthermore, it will discuss potential treatment goals and how the available data can be translated into treatment strategies in pediatric PAH.

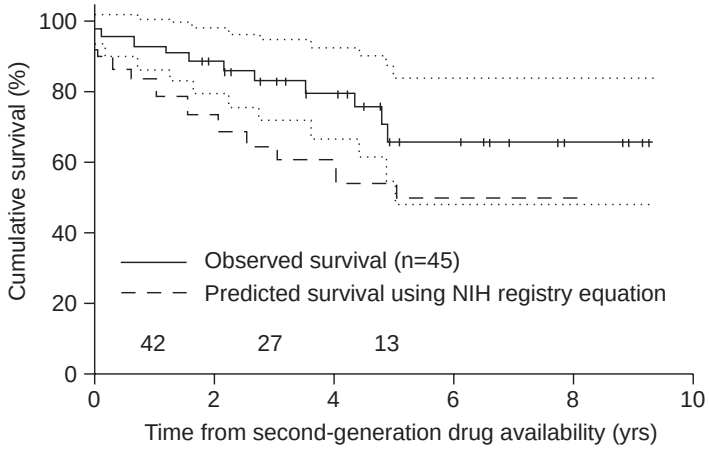

Figure 1. Survival of children with pulmonary arterial hypertension (PAH) since the introduction of PAH-targeted drugs compared with predicted survival.
Reproduced with permission from [23].

OVERVIEW OF CURRENTLY AVAILABLE TREATMENTS

Supportive treatments

In the era of PAH-targeted drugs, supportive therapies should not be forgotten. Many patients with PAH receive supportive treatments during their disease course, such as

anticoagulants and oxygen. Also, several general measures and lifestyle advices are often recommended and include influenza and pneumococcal immunization.[16]

Calcium channel blockers

Calcium channel blockers (CCBs) have been demonstrated to improve survival in a small select proportion (7%) of adults with IPAH and this has also been suggested in children.[25-27] The small proportion of IPAH patients who show a positive response to acute pulmonary vasodilator testing during cardiac catheterization will sustainably benefit from CCB therapy. For a long time, the proportion of responders has been assumed to be higher in children with IPAH than in adults. However, reported values in children vary significantly (8-56%) and appear to be highly dependent on the used response criteria.[24,25,27-29] In adults, responder status is usually determined according to criteria defined by Sitbon et al.[26] In children, criteria defined by Barst et al., either or not modified, are often used.[24,27,29] However, using the same criteria in both adults and children revealed similar proportions of responders in both age groups.[28] Responders treated with CCB therapy need frequent clinical and hemodynamic reevaluation as they may become non-responders over time and then need more advanced therapies. Due to negative inotropic effects, CCBs are advised not to be used in children <1 year of age.[30] In summary, CCBs are the drug of choice for children and adults who are identified as responders according to the Sitbon or Barst criteria.[1,30,31]

Prostanoids

Prostacyclin is an endogenous prostanoid which is produced by vascular endothelial cells. It is a potent vasodilator that has antiproliferative and anticoagulant effects as well. Prostacyclin production is decreased in PAH. The prostanoids are synthetic prostacyclin analogs and were the first discovered class of PAH-targeted drugs. Drug-related side effects are mainly related to systemic vasodilatation and include flushing, jaw pain, diarrhea, nausea and headache. Side effects related to the administration route are significant and include line infections for intravenous (IV), site pain for subcutaneous (SC) and bronchospasm, cough and chest pain for inhaled administration.

Epoprostenol improves clinical and hemodynamic conditions as well as survival in adults and children with PAH when compared to conventional therapies.[32-38] Epoprostenol therapy is possible at all ages, also in infants and toddlers. However, epoprostenol has a very short half-life and is unstable at room temperature, leading to several practical disadvantages including the need to be administered continuously intravenously through a central catheter. Also, it is generally advised to cool the epoprostenol cassette with ice packs. Intravenous administration poses the risk of line thrombosis and, more importantly, line infections that could lead to severe sepsis and death. Furthermore, these may lead to systemic embolic complications in patients with PAH associated with

congenital heart disease (PAH-CHD) and a right-to-left shunt. A sudden halt of administration may lead to possibly fatal rebound PH.[39]

Treprostinil has a longer half-life and is chemically stable at room temperature. It can thus be administered subcutaneously, inhaled and orally as well. In adults with PAH, positive effects have been shown for SC, IV and inhaled (TRIUMPH trial) treprostinil on exercise tolerance, clinical condition and hemodynamics.[40-45] Also, (a trend toward) improved survival has been reported for IV and SC treprostinil.[41-43] Oral treprostinil monotherapy was shown to improve exercise capacity after 12 weeks in adults (FREEDOM-M).[46] However, the addition of oral treprostinil to background therapy with a PDE-5 inhibitor, an ERA or both failed to improve exercise capacity after 16 weeks of therapy (FREEDOM C1/C2 trials).[47,48] Data regarding treprostinil therapy in children are limited. Because of the pain and inflammation at the puncture place, SC therapy has been thought not to be feasible in children. However, two small studies that included 8 and 29 children showed improvements in clinical condition and hemodynamics after add-on therapy with SC and inhaled treprostinil, respectively, without significant side effects. Both drugs appeared to have acceptable safety profiles.[49,50]

Beraprost was initially reported to improve clinical condition and hemodynamics in adults with PAH (ALPHABET trial), but these effects did not persist after a longer period of follow-up.[51-53]

Iloprost is mainly used as an inhaled prostanoid. Beneficial effects of inhaled iloprost as mono- or add-on therapy, which persisted until at least one year after treatment initiation, have been demonstrated in adults with PAH (AIR and STEP trials).[54-56] Some clinical improvements were reported in a proportion of children in two small single-center studies.[57,58] Switching to or addition of IV iloprost in adult patients, who clinically deteriorated on non-IV therapy, resulted in clinical and hemodynamic improvements only in a subgroup of these patients.[59-61]

Endothelin receptor antagonists

Endothelin-1 serum levels are increased in PAH patients.[62] Two receptors mediate endothelin-1 in humans: endothelin-A and endothelin-B receptors.[63] Both receptors are found in pulmonary vascular smooth muscle cells, where they promote vasoconstriction, inflammation and proliferation. Endothelin-B, however, is also present in pulmonary endothelial cells, where it mediates vasodilatation and activates antiproliferative agents. ERAs block these receptors, either both of them or the endothelin-A receptor selectively, and thereby inhibit the effects of endothelin-1. An advantage of selective over dual blocking or the other way around has not been demonstrated. The major side effects of ERAs are liver enzyme elevation, peripheral edema and a decrease in hemoglobin levels. ERAs for PAH are given orally and there are no major side effects related to the administration route.

Bosentan is a dual receptor antagonist that has been demonstrated to improve 6-minute walk distance (6MWD), World Health Organization functional class (WHO-FC) and time to clinical worsening in adults with PAH (BREATHE-1 trial).[64] Several uncontrolled pediatric studies, including 19-101 children, suggested similar effects. Importantly, bosentan appeared to be well tolerated and safe in children and a pediatric formulation is available.[21,22,65-68] Elevation of liver enzymes appears to occur less frequently in children than in adults (3% versus ~10%).[1,22,69,70] Nonetheless, regular testing remains necessary as elevations require dose adaptation or discontinuation of bosentan.

Ambrisentan is a selective endothelin-A receptor antagonist that has demonstrated effects comparable to bosentan (ARIES trials).[71-74] A retrospective study in 38 children suggested that ambrisentan may have beneficial effects in a subset of children with PAH. Furthermore, ambrisentan may have a favorable safety profile compared to bosentan, including less liver function abnormalities and less drug interactions.[75]

Macitentan, a dual receptor antagonist with sustained receptor binding and increased tissue penetration, was recently shown to significantly reduce morbidity when compared to placebo in 742 PAH patients aged >12 years (SERAPHIN trial).[76,77] Clinical and hemodynamic parameters improved after 6 months of therapy compared to placebo. Macitentan had a favorable safety profile with little occurrence of liver enzymes elevation and peripheral edema.[77] To date, no data are available in children.

PDE-5 inhibitors

PDE-5 inactivates cyclic guanosine monophosphate through which NO mediates its vasodilatory and antiproliferative effects. The PDE-5 inhibitors inhibit the actions of PDE-5, and thus increase the effects of available NO. The most common side effects are related to systemic vasodilatation and include headache, flushing and epistaxis. In general, PDE-5 inhibitors for PAH are given orally and there are no major side effects related to the administration route.

Sildenafil has been shown to have beneficial effects in adults with PAH that persist up to 3 years after start of therapy (SUPER trials). Also, sildenafil treatment was well tolerated.[78,79] STARTS-1 was the first randomized, double-blind, placebo-controlled study ever in children with PAH. Although the beneficial effect on the primary endpoint of the study, peak oxygen consumption on cardiopulmonary exercise testing (CPET), just failed to reach statistical significance, the results showed improvements in hemodynamics in the medium- and high-dose sildenafil-treated groups.[80] The recently published results of the subsequent STARTS-2 trial suggested worse survival in children receiving high doses of sildenafil.[81] However, the data were not conclusive. This is illustrated by the fact that these data caused the United States Food and Drug Administration to recommend against the use of sildenafil in children, whereas the European Medicines Agency approved the use of sildenafil in children with a warning against high doses of sildenafil.

The American Pediatric Pulmonary Hypertension Network stated that 'although we believe that low doses of sildenafil are likely to be safe in pediatric PAH and we support the EMA finding, further studies should carefully examine its role in the long-term therapy of children'.[82]

Tadalafil has been demonstrated to improve exercise tolerance and hemodynamics and to lead to better quality of life and increased time to clinical worsening after 16 weeks of therapy in treated adults compared to placebo (PHIRST trial).[83] Improved exercise tolerance was maintained after another 52 weeks.[84] Tadalafil treatment was safe and well tolerated. Pediatric data regarding tadalafil are scarce. One retrospective, single-center cohort study was performed that included 33 children who either transitioned from sildenafil to tadalafil (29 patients) or received tadalafil as initial PDE-5 inhibitor therapy (4 patients). Transition to tadalafil improved mPAP, indexed PVR and pulmonary-to-systemic vascular resistance ratio, while exercise capacity, brain natriuretic peptide (BNP) and cardiac index did not significantly change. Clinical and hemodynamic conditions tended to improve in the 4 patients who received initial tadalafil therapy. Tadalafil appeared to be safe and well tolerated.[85]

Vardenafil is a new PDE-5 inhibitor that has been shown to improve exercise tolerance and hemodynamics after 3 and 14 months when compared to baseline and after 12 and 24 weeks when compared to baseline and placebo in 45 and 66 adult PAH patients, respectively (EVALUATION trial). Side effects were mild and mostly transient.[86,87] To date, no data are available in children.

Novel drugs

Riociguat, a soluble guanylate cyclase stimulator, is a novel drug that acts more upstream in the NO pathway than the PDE-5 inhibitors. Riociguat increases cyclic guanosine monophosphate availability by directly stimulating soluble guanylate cyclase. Its actions can be synergetic with NO, but it can also act completely independent of NO. Riociguat improved exercise capacity, clinical condition and hemodynamics in PAH patients after 12 weeks of therapy compared to baseline and placebo (PATENT trial).[10] To date, no data are available in children.

Selexipag is an oral selective prostacyclin receptor agonist. A Phase II study including 43 adult PAH patients on stable background therapy showed that PVR improved after 17 weeks of addition of selexipag and that it was well tolerated.[11] Phase III clinical trial results are currently pending (GRIPHON trial). To date, no data are available in children.

Imatinib is a tyrosine kinase inhibitor that was initially developed for the treatment of chronic myeloid leukemia. It inhibits vascular smooth muscle cell proliferation and hyperplasia.[88] Thus, unlike the previously described drugs targeting the three major pathways, imatinib has mainly antiproliferative effects. Imatinib was shown to have beneficial effects in patients with severe PAH.[89,90] However, more discontinuations and

serious adverse events (including subdural hematoma) were reported in the imatinib group compared to placebo.[90] Consequently, the authorization application for imatinib in PAH was withdrawn. There are no data regarding imatinib in pediatric PAH.

Several novel drugs targeting newly identified pathways in the pathogenesis of PAH are currently under investigation and may be promising drugs for the future. These include *rho kinase inhibitors* targeting the Rho/Rho-kinase signaling pathway, which influences many cellular actions including apoptosis, inflammation and vasoconstriction[91] and *endothelial progenitor cells* targeting regeneration and repair of damaged lung microvasculature.[92,93]

Combination therapies

The rationale behind combination therapy is that the PAH-targeted drugs target three different pathways and that simultaneous targeting of two or three of these pathways may lead to a greater beneficial effect than targeting only one pathway. The current guidelines for the treatment of adults with PAH summarize options for treatment initiation.[1,31] The level of evidence and recommendation for the use of combination therapies has significantly improved since controlled data on such use are becoming increasingly available, although this evidence is almost exclusively based on adult studies.[31]

Since the early 2000s, various studies on the effects of combination or add-on therapy in PAH have been performed.

The combination of an ERA and a PDE-5 inhibitor has been shown to (tend to) improve exercise capacity, functional status and hemodynamics in adults compared to monotherapy with one of these drugs.[83,94-98] Also, the addition of macitentan to PDE-5 inhibitor therapy improved time to the combined endpoint, including worsening of PAH, lung transplantation (LTx), escalation to IV or SC prostanoids and death (SERAPHIN trial).[77] Combining both classes appeared to be safe and well tolerated in all studies. Add-on riociguat to ERA or non-IV prostanoid therapy was shown to be beneficial and safe in the PATENT trial.[10]

Combining prostanoids with either ERAs or PDE-5 inhibitors has been studied in different compositions. Add-on sildenafil therapy in adults receiving long-term IV epoprostenol improved clinical and hemodynamic conditions and time to clinical worsening (PACES trial).[99] Add-on therapy with inhaled treprostinil or inhaled iloprost to ERA and/or PDE-5 inhibitor therapy was studied in adults who did not improve on oral therapy alone (TRIUMPH and STEP trials). Both were shown to improve exercise capacity, functional status and hemodynamics.[44,55,100] Furthermore, inhaled iloprost was shown to prolong time to clinical worsening and the beneficial effects of inhaled treprostinil were shown to persist for 24 months.[45,55] Beneficial results have also been reported for the addition of bosentan to SC treprostinil therapy.[101]

Thus, several studies have shown beneficial effects of add-on combination therapy in adult PAH patients who did not adequately respond to monotherapy. Little research has been done regarding this subject in children. A recently published report, including 275 children, showed that children who received combination therapy during the study period had better survival compared to children who received monotherapy, independent of disease characteristics at baseline.[25] Another recent report, including 24 children, showed that the addition of sildenafil to bosentan improved WHO-FC and 6MWD in children who clinically deteriorated on bosentan mono therapy.[102] Survival seemed to improve in the children who received add-on sildenafil therapy compared to those who remained on bosentan therapy alone. Add-on therapy with inhaled or SC treprostinil was shown to improve clinical and hemodynamic conditions in children with severe PAH.[49,50] These results point in the same direction as those obtained in adult studies, supporting the beneficial effects of add-on combination therapy in pediatric PAH.

Although combination therapy seems to be efficacious in both adults and children with PAH, it remains unclear when and how to start combination therapy and what disease characteristics could guide decisions regarding therapy escalation.

Non-drug treatments

Non-drug treatments could be considered to preserve cardiac output and to reduce the right ventricular (RV) workload. They could serve as a treatment option to relieve symptoms or as a bridge to LTx.

Balloon atrial septostomy (BAS) is used in patients with IPAH and end-stage disease, recurrent syncope or both. As syncope is more frequent in the pediatric age group, BAS could be more often of use in children than in adults. BAS is believed to lead to an increase of left ventricle preload and cardiac output at the cost of a decrease in systemic arterial oxygen saturation. This overall is assumed to result in increased systemic oxygen transportation. Several small uncontrolled studies including adults and/or children reported improvements in clinical and hemodynamic conditions. BAS has been suggested to improve survival as well, increasing the chance of receiving donor lungs.[103-107] BAS requires an invasive procedure, which brings concomitant risks, especially in this vulnerable population. In patients with severely elevated right atrial pressure (RAP), the mortality rate increases due to potential major right-to-left shunting with life-threatening hypoxemia. Thus, it has been advised not to wait with BAS until this hemodynamic condition develops.[1,31]

Potts shunt, a (direct) anastomosis between the left pulmonary artery and the descending aorta, forms an alternative way to create a pulmonary-to-systemic shunt and, when compared to BAS, has the advantage of directly relieving the right ventricle. This technique is suitable for patients with suprasystemic pulmonary pressures and can also be used in patients with concomitant severely elevated RAP. The decrease in oxygen

saturation will only occur in the lower body half. Two case reports of both two children and one retrospective multicenter study of eight children with end-stage IPAH showed improved functional and exercise capacity, lower plasma levels of BNP and improved RV function in both the short- and longer-term.[108-110] However, postoperative mortality in this early experience was reported to be 25% in the multicenter study, illustrating the high risk of invasive procedures in PAH patients. Further research including more patients is essential to evaluate the short- and long-term effects of this palliative procedure.

Aortic banding is based upon the theory of ventricular-ventricular interaction, in which right heart disease alters left ventricular function and vice versa. A recent experimental study including 23 rabbits showed that aortic constriction in a model of chronic RV pressure overload resulted in improved biventricular function and myocardial remodeling.[111] To date, no studies in humans exist and its possible value in (pediatric) patients with PAH remains to be elucidated.

(Heart-)LTx remains the treatment of choice for end-stage PAH despite maximal therapy. As the heart has the ability to recover and re-remodel to normal function and dimensions, bilateral LTx is most frequently performed. In children, IPAH is the second most common indication for LTx.[112] Given the high risk and major consequences of the procedure, LTx is only indicated in patients with progressive and severe PAH despite maximal medical therapy. Several small studies including children with IPAH that underwent bilateral LTx showed improved WHO-FC, improved RV function and improved survival, with a median survival that ranged from 45 to 70 months.[113-115] Reported survival was comparable or improved compared to LTx in children with cystic fibrosis.[112] Whether a child is eligible for transplantation and what the optimal timing is remains unknown and is mostly determined by the center's expert opinion and donor organ availability. Although medical treatment options are expanding and seem to be beneficial, medical therapy should not lead to (too) late listing for LTx.

In summary, over the past 15 years, many RCTs showed that PAH-targeted drugs are efficacious in the treatment of PAH in adult patients. Although mainly uncontrolled, observational studies exist in children with PAH, the available data suggest comparable effects. The available PAH-targeted drugs appear to have acceptable safety and tolerability profiles also in children, except for sildenafil in which this is a subject of debate. Combination therapy with PAH-targeted drugs that act on different pathways could lead to additional beneficial clinical effects, also in pediatric PAH. Novel drugs targeting existing or newly discovered pathways in the pathogenesis of PAH are being developed and will hopefully further improve quality of life and survival in pediatric PAH. Furthermore, non-drug treatments are available for children and are believed to have a place in treatment strategies for children with PAH.

TREATMENT STRATEGIES

Although the development of novel drugs for the treatment of PAH is of great importance, knowledge on how to use the various drugs combined in optimal treatment strategies is at least as important. To improve survival and optimize quality of life in patients with PAH, relevant considerations include choice of drugs, timing of therapy initiation and when and how to use combination therapy. For example, guidelines recommend combination therapy 'in case of inadequate clinical response'. However, how should inadequate clinical response be defined?

A goal-oriented treatment strategy is now recommended to guide therapy in adult PAH patients.[31] Instead of reacting on deterioration of a patient's clinical condition, the physician aims to reach a predefined improvement in clinical condition.[116] Thus, patients who start therapy are supposed to reach certain goals.[1,117,118] If these goals are not met within 3-6 months, therapy should be escalated. For such a strategy, it is essential to have reliable, validated and clinically meaningful treatment goals that are applicable in all patients and that can be obtained without disproportional risks.

The treatment of patients with PAH aims at improving quality of life and survival. Therefore, a treatment goal could be a measure that represents improved quality of life, for instance relieve of symptoms or improvement of exercise capacity. Also, a treatment goal could be a clinical measure that represents a decrease in the chance of an outcome event, such as death or LTx. Thus, a variable that serves as a treatment goal either directly reflects quality of life or meets the following criteria for a surrogate for outcome: has a strong correlation with outcome, values can be influenced by therapy and treatment-induced changes reflect a change in outcome.[119,120] Thus, a variable that serves as treatment goal is not simply a predictor of outcome. It should additionally be influenced by therapy. To illustrate this, although patient characteristics as age and sex are reported to predict outcome, it is obvious that these are no suitable treatment goals. The third requirement for a treatment goal indicates that a treatment-induced change in the variable should reflect a change in outcome. For example, improved WHO-FC after 6 months of therapy should be associated with improved survival. Follow-up assessments are therefore necessary.

Several clinical, biochemical and hemodynamic variables have been identified as predictors of outcome both in adults and children with PAH (Table 1). However, data on the predictive value of treatment-induced changes in these predictors are scarce. Few observational studies regarding treatment-induced changes in adults have been published.[121-124] Very few data are currently available in children. Although the concept of goal-oriented treatment seems reasonable and beneficial, these variables should be sufficiently validated as treatment goals in the relevant patients, so also in children with PAH.

Table 1. Evidence for the prognostic value of potential treatment goals in children with pulmonary arterial hypertension

	Prognostic Implications at Baseline (Ref.)	Prognostic Implications at Follow-Up (Ref.)
Clinical condition		
WHO-FC	7, 21, 22, 23, 25, 126, 127	160
6MWD	126	-
CPET	-	-
Biomarkers		
(NT-pro)BNP	23, 24, 25, 36, 141, 142, 143	160
Imgaging		
Echocardiography	126, 146, 147	161
CMR	148	-
Hemodynamics		
mRAP	25, 27	-
PRVi	22, 24, 25, 27, 126, 131	-
mPAP/mSAP	23, 25, 28, 127	-
CI	23, 24, 25, 27	-
Pulsatile components of RV afterload	127, 131	-

6MWD, six-minute walk distance; CI, cardiac index; CMR, cardio magnetic resonance; CPET, cardiopulmonary exercise testing; mPAP/mSAP, mean pulmonary-to-systemic arterial pressure ratio; mRAP, mean right atrial pressure; (NT-pro)BNP, (N-terminal pro) brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RV, right ventricular; WHO-FC, World Health Organization functional class.

Current treatment goals in adult patients, as recently proposed at the 5th World Symposium on Pulmonary Hypertension (WSPH) held in Nice 2013, to optimize prognosis in patients with PAH include WHO-FC I-II, near-normal or normal RV size and function on echocardiography or cardiac magnetic resonance (CMR), RAP <8 mmHg and cardiac index >2.5 to 3.0 l/min/m^2 on cardiac catheterization, 6MWD >380 to 440 m, peak oxygen consumption >15 ml/min/kg on CPET and normal plasma levels of N-terminal pro brain natriuretic peptide (NT-proBNP) or BNP.[117] Based on the strength of expert opinion, the pediatric task force of the 5th WSPH proposed a treatment algorithm for children with IPAH in which patients are characterized using a risk profile based on proposed pediatric treatment goals.[30] An adapted version of this risk profile is shown in Table 2.

Table 2. Treatment goals proposed for guiding therapy in children with pulmonary arterial hypertension.

Lower Risk	Treatment targets	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I, II	WHO-functional class	III, IV
Minimally elevated	Serum BNP/NT-proBNP	Significantly elevated, rising level
	Echocardiography	Severe RV enlargement/ dysfunction
		Pericardial effusion
Systemic CI >3.0 l/min/m^2	Hemodynamics	Systemic CI <2.5 l/min/m^2
mPAP/mSAP <0.75		mPAP/mSAP >0.75
Acute vasoreactivity		mRAP >10 mmHg PVRi >20 WU.m^2
Stable >450 m	6MWD*	≤350 m or decreasing

* Although the 6MWD was not proposed as treatment goal, maintaining of or improving to an adequate 6MWD can be regarded as clinically meaningful in pediatric PAH, as improved exercise capacity is believed to improve quality of life. 6MWD, six-minute walk distance; BNP, brain natriuretic peptide; CI, cardiac index; mPAP/mSAP, mean pulmonary-to-systemic arterial pressure ratio; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RV, right ventricular.
Adapted with permission from [30].

In the following section, variables that may serve as treatment goals in children with PAH will be discussed and the relevant evidence will be reviewed.

Clinical characteristics of PAH in children include symptoms, such as dyspnea at rest and/or during exercise, exercise intolerance, syncope, fatigue and chest pain, that could greatly impact quality of life. Reducing these symptoms is clinically relevant, will improve quality of life and thus can be regarded as a valid treatment goal in children with PAH. Children with PAH may show failure to thrive.[6,7,17] Lower age-normalized scores for height and weight have been suggested to correlate with worse survival.[7] However, this could not be confirmed in two other cohorts.[24,25] Furthermore, no catch-up growth after treatment initiation was found, which potentially disqualifies growth, or age-normalized scores for height and weight, as treatment goals.[7]

Although a negative correlation between syncope and survival has not been confirmed in several pediatric studies, the occurrence of syncope or its persistence after treatment initiation is regarded as a serious sign of disease and according to current expert opinion requires escalation of therapy.[7,24,30]

WHO-FC is a non-invasive, subjective assessment of a patient's clinical condition using the occurrence of symptoms at different levels of activities. WHO-FC, both at baseline as

well as after treatment, has been shown to strongly correlate with survival in adult PAH patients.[121-123] It therefore represents a useful treatment goal to guide therapy in adults. WHO-FC can be difficult to assess in infants and young children as it will be based on the observation and impression of caregivers. An age-adjusted estimation of a child's physical activity in relation to its peers may help to accurately determine WHO-FC. Despite this apparent limitation, several pediatric studies have shown WHO-FC to be a strong predictor of outcome that could be affected by therapy.[7,21-23,25,125-127] A functional classification system specifically designed for children has been proposed but has not been validated yet.[128] Overall, WHO-FC is an easy and freely obtainable parameter reflecting clinical condition also in children. As in adult PAH, the WSPH pediatric task force proposed reaching or maintaining WHO-FC I or II as a treatment goal in pediatric PAH.

Six-minute walk distance is widely used to assess clinical condition in adult PAH. It has served as primary endpoint in most RCTs. A meta-analysis recently showed that changes in 6MWD may not reflect changes in outcome.[129] The use of 6MWD in children is limited due to developmental restrictions: infants do not walk, young children may be distracted during the test and developmental delays may affect the test results. In general, it is a reliable and reproducible test that can be performed from an age of 7 years.[130] However, many children are younger than 7 years at diagnosis.[6,7,22] The predictive value of 6MWD for outcome in children with PAH is unclear and available data from various observational studies are contradictory on this point.[25,126,131] Nevertheless, as in adults, 6MWD can be improved by therapies in children with PAH.[49,50,57,65,66,102] Since improved exercise capacity is believed to improve quality of life, maintaining of or improving to an adequate 6MWD can be regarded as a valid treatment goal in pediatric PAH.

Cardiopulmonary exercise testing has been shown to predict survival in adults with PAH.[132,133] Treatment-induced changes have not been studied. In young children, the use of CPET is also hampered by limited feasibility due to developmental issues. Reference values are available for children from an age of 6-8 years.[134,135] Peak oxygen consumption was shown to correlate with mPAP and PVR in 40 children with PAH.[136] Also, CPET has been suggested to provide complimentary information to the 6MWT.[137] A possible correlation between CPET and survival in children with PAH has not been studied. Overall, its value in a goal-oriented treatment strategy in children remains unknown.

NT-proBNP and BNP are biomarkers related to RV dysfunction, which is one of the most important predictors for survival in PAH.[3] Both in adults and children, plasma levels of (NT-pro)BNP have been shown to strongly correlate with survival.[23,25,36,138-143] Recently, treatment-induced changes in NT-proBNP were shown to be associated with a change in survival in adults, making NT-proBNP a valid treatment goal.[121] In children with PAH, changes in (NT-pro)BNP levels have been correlated with changes in WHO-FC, 6MWD and hemodynamics.[141-144] Although the correlation between treatment-induced changes of (NT-pro)BNP and survival has not been studied yet, the WSPH pediatric task force

proposed reaching (near-)normal levels of (NT-pro)BNP as treatment goal and advised (NT-pro)BNP to be part of the regular follow-up in pediatric PAH.

Echocardiography and CMR are both non-invasive methods to assess RV function. In adults and children with PAH, echocardiographic and CMR parameters at baseline have been associated with survival.[126,139,145-150] Furthermore, treatment-induced changes in CMR parameters were shown to predict survival in adult patients.[149] Although data are promising, they remain currently limited and further research is necessary to determine the value of echocardiography and CMR in guiding treatment in PAH patients. According to the WSPH pediatric task force, the findings of severe or progressive RV dysfunction or pericardial effusion dictates escalation of therapy.

Hemodynamic parameters are objective and can be obtained at any age. In adults, hemodynamics at baseline have been shown to predict survival.[3,121,123,139,151-153] Treatment-induced changes in cardiac index and mixed venous oxygen saturation were recently reported to correlate with changes in survival, supporting their use as treatment goals.[121] Hemodynamic variables, such as RAP, indexed PVR, cardiac index and mean pulmonary-to-systemic arterial pressure ratio, have been associated with survival in the pediatric age group.[22-25,27,28,126,127] Furthermore, initiation of therapy has been shown to improve hemodynamics.[21,27,154,155] Recently, pulsatile components of RV afterload were shown to predict survival in children with PAH, as in adults.[127,131,156] Although it seems reasonable to assume that treatment-induced improvements in hemodynamics will lead to a better outcome, these remain to be demonstrated in pediatric PAH. Furthermore, obtaining invasive hemodynamics by cardiac catheterization often requires the use of sedation or general anesthesia in childhood, which comes with associated risks. Cardiac catheterizations in pediatric PAH carried out in specialized centers are reported to have a complication rate (major complications) of 4-6%.[157-159] Nevertheless, the WSPH pediatric task force proposed hemodynamic variables as potential treatment goals. Many, but not all, expert centers for pediatric PAH practice a strategy of repeated cardiac catheterizations during follow-up, with the rationale that the risks of cardiac catheterization, if minimized via adequate expertise of the treatment team, will be outweighed by the benefits of optimizing therapy and improvement of outcome.

In summary, although outcome in pediatric PAH has improved since the introduction of PAH-targeted drugs, survival of children with this disease is still unsatisfactory. Improvement in treatment success is highly needed and waiting for clinical deterioration to escalate initiated therapy may not be the way to go. Therefore, goal-oriented treatment strategies are currently adopted in the management of pediatric PAH. Taking into account the paucity of data on treatment goals in children with PAH, the WSPH pediatric task force agreed on recommending several variables to serve as treatment goals, including clinical symptoms, WHO-FC, (NT-pro)BNP, RV imaging and invasive he-

modynamics. However, proper validation of these variables as treatment goals remains to be done.

EXPERT COMMENTARY

Although several PAH-targeted drugs have been developed and their efficacy has been demonstrated, outcome in children with PAH remains poor. Therefore, there is a high, but unmet, need for better treatment strategies specifically for children. Knowing how to adequately assess treatment response and when and how to escalate therapy is essential. Emerging evidence is becoming available that children with PAH may benefit from adequate monitoring of treatment response and more aggressive treatment regimens with escalation to combination therapy.

Ideally, pediatric data for evidence-based guidelines, that is, RCTs, should be collected. However, controlled trials in pediatric PAH were and will be hampered by difficulties. First, it is challenging to reach appropriate study sizes due to the rarity and heterogeneity of the disease. Second, the widespread pediatric use of currently available PAH-targeted drugs complicates study designs. Several PAH-targeted drugs are regarded 'standard of care', while not approved for children. Third, there is a lack of validated endpoints in pediatric PAH, including the non-acceptance by the regulatory authorities of invasive hemodynamics as endpoint. Therefore, much of the pediatric data will have to be derived from clinical registries and cohorts that collect patient and treatment characteristics and outcome data. A standardized follow-up, with predefined variables and timepoints, would be very helpful. Registries may be multicenter, multicountry center-based, such as the TOPP and REVEAL registries. They may also be based on national cohorts, such as the Dutch and United Kingdom national service registries. Furthermore, there are single-center registries. All these registries, each with its unique design and thereby having its own merits and disadvantages, and providing mostly observational data, will have to clearly define their aims and collect relevant data. Only then, registries will be able to contribute to the actual questions that arise in defining the optimal management of children with different types of PAH in the coming future.

One of these questions is whether children with IPAH and children with PAH-CHD should be treated equally. Most of the studies regarding PAH-specific therapies have been performed in patients with IPAH. Nevertheless, an increasing amount of data is becoming available showing that these drugs, perhaps with the exception of CCBs, have similar effects in both groups. The same holds for clinical predictors of outcome. Furthermore, although survival of patients with PAH-CHD has long been assumed to be more favorable than survival of patients with IPAH, recent data indicate that in childhood survival is equally poor in both types of PAH. Based on current knowledge, the authors

feel that there is no indication to treat children with PAH-CHD according to different treatment algorithms than children with IPAH. Nevertheless, practical issues should be considered for the individual patient, such as the use of central catheters in patients with a right-to-left shunt.

Importantly, defining clinically relevant treatment goals that correlate with long-term outcome has emerged as one of the most critical tasks. Effort should be put in establishing and validating these treatment goals, which will help to guide therapy and improve the currently unsatisfying outcome in pediatric PAH.

FIVE-YEAR VIEW

In the next five years, treatment options for patients with PAH will likely expand. More drugs, targeting new pathways, will become available and have to be evaluated in RCTs. 'Smart-design' controlled trials should be designed to collect evidence for efficacy in the pediatric PAH population. Also, the value of non-drug treatments should be established within the setting of drug treatment. Especially the role of the Potts shunt in short- and long-term outcome of pediatric PAH will have to be investigated. Since experience in this technique is limited and patient numbers are small, a multicountry registry for this intervention could be very valuable.

In the coming years, data from newly or redesigned registries will become available that will allow for the assessment and validation of the recently proposed treatment goals and the identification of new treatment goals. With these, evidence-based guidelines that define how to accurately monitor treatment response and escalate therapy will be developed also for children. Finally, novel therapies directed toward the reversal of RV dysfunction in PAH may become available.

REFERENCES

1. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS), endorsed by the international society of heart and lung transplantation (ISHLT). Eur Heart J. 2009;30(20):2493-2537.
2. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):13S-24S.
3. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. results from a national prospective registry. Ann Intern Med. 1991;115(5):343-349.
4. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in france: Results from a national registry. Am J Respir Crit Care Med. 2006;173(9):1023-1030.
5. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. Eur Respir J. 2007;30(1):104-109.
6. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
7. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
8. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest. 2008;118(7):2372-2379.
9. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351(14):1425-1436.
10. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013;369(4):330-340.
11. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J. 2012;40(4):874-880.
12. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation. 2002;106(12):1477-1482.
13. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J. 2005;25(2):244-249.
14. Rosenzweig EB, Widlitz AC, Barst RJ. Pulmonary arterial hypertension in children. Pediatr Pulmonol. 2004;38(1):2-22.
15. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: A comparison between children and adults. Eur Respir J. 2011;37(3):665-677.
16. Berger RM, Bonnet D. Treatment options for paediatric pulmonary arterial hypertension. Eur Respir Rev. 2010;19(118):321-330.
17. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
18. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
19. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.
20. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: Complex presentation and diagnosis. J Pediatr. 2009;155(2):176-82.e1.

21. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(4):697-704.
22. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
23. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
24. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
25. ZijIstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
26. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-3111.
27. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
28. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: Occurrence and prognostic value when comparing three response criteria. Eur Heart J. 2011;32(24):3137-3146.
29. Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest. 1986;89(4):497-503.
30. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
31. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D60-72.
32. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296-301.
33. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132(6):425-434.
34. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med. 1998;338(5):273-277.
35. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation. 2002;106(12):1477-1482.
36. Nakayama T, Shimada H, Takatsuki S, et al. Efficacy and limitations of continuous intravenous epoprostenol therapy for idiopathic pulmonary arterial hypertension in japanese children. Circ J. 2007;71(11):1785-1790.
37. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99(14):1858-1865.
38. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). results of a randomized trial. Ann Intern Med. 1990;112(7):485-491.

39. Barst R. How has epoprostenol changed the outcome for patients with pulmonary arterial hypertension? Int J Clin Pract Suppl. 2010;(168):23-32. doi(168):23-32.
40. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165(6):800-804.
41. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28(6):1195-1203.
42. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest. 2006;129(6):1636-1643.
43. Hiremath J, Thanikachalam S, Parikh K, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: A placebo-controlled trial. J Heart Lung Transplant. 2010;29(2):137-149.
44. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: A randomized controlled clinical trial. J Am Coll Cardiol. 2010;55(18):1915-1922.
45. Benza RL, Seeger W, McLaughlin VV, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: The treprostinil sodium inhalation used in the management of pulmonary arterial hypertension (TRIUMPH) study open-label extension. J Heart Lung Transplant. 2011;30(12):1327-1333.
46. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: A randomized, controlled trial. Circulation. 2013;127(5):624-633.
47. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): A randomized controlled trial. Chest. 2012;142(6):1383-1390.
48. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): A randomized controlled trial. Chest. 2013;144(3):952-958.
49. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr. 2011;158(4):584-588.
50. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. Am J Cardiol. 2012;110(11):1704-1709.
51. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2003;41(12):2119-2125.
52. Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: A randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2002;39(9):1496-1502.
53. Nagaya N, Uematsu M, Okano Y, et al. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. J Am Coll Cardiol. 1999;34(4):1188-1192.
54. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347(5):322-329.

55. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006;174(11):1257-1263.
56. Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med. 2000;342(25):1866-1870.
57. Alehan D, Yildirim I, Sahin M, Ozkutlu S, Ozer S, Karagoz T. Long-term inhaled iloprost use in children with pulmonary arterial hypertension. Cardiol Young. 2012;22(4):396-403.
58. Ivy DD, Doran AK, Smith KJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;51(2):161-169.
59. Hoeper MM, Spiekerkoetter E, Westerkamp V, Gatzke R, Fabel H. Intravenous iloprost for treatment failure of aerosolised iloprost in pulmonary arterial hypertension. Eur Respir J. 2002;20(2):339-343.
60. Knudsen L, Schurawlew A, Nickel N, et al. Long-term effects of intravenous iloprost in patients with idiopathic pulmonary arterial hypertension deteriorating on non-parenteral therapy. BMC Pulm Med. 2011;11:56-2466-11-56.
61. Ewert R, Opitz CF, Wensel R, Winkler J, Halank M, Felix SB. Continuous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Clin Res Cardiol. 2007;96(4):211-217.
62. Yoshibayashi M, Nishioka K, Nakao K, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. evidence for increased production of endothelin in pulmonary circulation. Circulation. 1991;84(6):2280-2285.
63. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res. 2004;61(2):227-237.
64. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896-903.
65. Maiya S, Hislop AA, Flynn Y, Haworth SG. Response to bosentan in children with pulmonary hypertension. Heart. 2006;92(5):664-670.
66. Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J. 2011;38(1):70-77.
67. Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther. 2003;73(4):372-382.
68. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: The FUTURE-1 study. Br J Clin Pharmacol. 2009;68(6):948-955.
69. Beghetti M, Hoeper MM, Kiely DG, et al. Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: Results from the european postmarketing surveillance program. Pediatr Res. 2008;64(2):200-204.
70. Beghetti M. Bosentan in pediatric patients with pulmonary arterial hypertension. Curr Vasc Pharmacol. 2009;7(2):225-233.
71. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(3):529-535.
72. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117(23):3010-3019.

73. Oudiz RJ, Galie N, Olschewski H, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54(21):1971-1981.
74. Klinger JR, Oudiz RJ, Spence R, Despain D, Dufton C. Long-term pulmonary hemodynamic effects of ambrisentan in pulmonary arterial hypertension. Am J Cardiol. 2011;108(2):302-307.
75. Takatsuki S, Rosenzweig EB, Zuckerman W, Brady D, Calderbank M, Ivy DD. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr Pulmonol. 2013;48(1):27-34.
76. Gatfield J, Mueller Grandjean C, Sasse T, Clozel M, Nayler O. Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. PLoS One. 2012;7(10):e47662.
77. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809-818.
78. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148-2157.
79. Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: The SUPER-2 study. Chest. 2011;140(5):1274-1283.
80. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012;125(2):324-334.
81. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014.
82. Abman SH, Kinsella JP, Rosenzweig EB, et al. Implications of the U.S. food and drug administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. Am J Respir Crit Care Med. 2013;187(6):572-575.
83. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119(22):2894-2903.
84. Oudiz RJ, Brundage BH, Galie N, et al. Tadalafil for the treatment of pulmonary arterial hypertension: A double-blind 52-week uncontrolled extension study. J Am Coll Cardiol. 2012;60(8):768-774.
85. Takatsuki S, Calderbank M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. Pediatr Cardiol. 2012;33(5):683-688.
86. Jing ZC, Jiang X, Wu BX, et al. Vardenafil treatment for patients with pulmonary arterial hypertension: A multicentre, open-label study. Heart. 2009;95(18):1531-1536.
87. Jing ZC, Yu ZX, Shen JY, et al. Vardenafil in pulmonary arterial hypertension: A randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med. 2011;183(12):1723-1729.
88. Barst RJ. PDGF signaling in pulmonary arterial hypertension. J Clin Invest. 2005;115(10):2691-2694.
89. Ghofrani HA, Morrell NW, Hoeper MM, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med. 2010;182(9):1171-1177.
90. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: Results of the randomized IMPRES study. Circulation. 2013;127(10):1128-1138.
91. Fukumoto Y, Yamada N, Matsubara H, et al. Double-blind, placebo-controlled clinical trial with a rho-kinase inhibitor in pulmonary arterial hypertension. Circ J. 2013;77(10):2619-2625.

92. Zhu JH, Wang XX, Zhang FR, et al. Safety and efficacy of autologous endothelial progenitor cells transplantation in children with idiopathic pulmonary arterial hypertension: Open-label pilot study. Pediatr Transplant. 2008;12(6):650-655.
93. Smadja DM, Gaussem P, Mauge L, et al. Circulating endothelial cells: A new candidate biomarker of irreversible pulmonary hypertension secondary to congenital heart disease. Circulation. 2009;119(3):374-381.
94. Hoeper MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. Eur Respir J. 2004;24(6):1007-1010.
95. D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and eisenmenger physiology. Int J Cardiol. 2012;155(3):378-382.
96. Lunze K, Gilbert N, Mebus S, et al. First experience with an oral combination therapy using bosentan and sildenafil for pulmonary arterial hypertension. Eur J Clin Invest. 2006;36 Suppl 3:32-38.
97. Porhownik NR, Al-Sharif H, Bshouty Z. Addition of sildenafil in patients with pulmonary arterial hypertension with inadequate response to bosentan monotherapy. Can Respir J. 2008;15(8):427-430.
98. Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. Eur Respir J. 2007;29(3):469-475.
99. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: A randomized trial. Ann Intern Med. 2008;149(8):521-530.
100. Channick RN, Olschewski H, Seeger W, Staub T, Voswinckel R, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. J Am Coll Cardiol. 2006;48(7):1433-1437.
101. Benza RL, Rayburn BK, Tallaj JA, Pamboukian SV, Bourge RC. Treprostinil-based therapy in the treatment of moderate-to-severe pulmonary arterial hypertension: Long-term efficacy and combination with bosentan. Chest. 2008;134(1):139-145.
102. Douwes JM, Roofthooft MT, Van Loon RL, et al. Sildenafil add-on therapy in paediatric pulmonary arterial hypertension, experiences of a national referral centre. Heart. 2014;100(3):224-230.
103. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation. 1995;91(7):2028-2035.
104. Thanopoulos BD, Georgakopoulos D, Tsaousis GS, Simeunovic S. Percutaneous balloon dilatation of the atrial septum: Immediate and midterm results. Heart. 1996;76(6):502-506.
105. Micheletti A, Hislop AA, Lammers A, et al. Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension. Heart. 2006;92(7):969-972.
106. Law MA, Grifka RG, Mullins CE, Nihill MR. Atrial septostomy improves survival in select patients with pulmonary hypertension. Am Heart J. 2007;153(5):779-784.
107. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol. 1998;32(2):297-304.
108. Blanc J, Vouhe P, Bonnet D. Potts shunt in patients with pulmonary hypertension. N Engl J Med. 2004;350(6):623.
109. Labombarda F, Maragnes P, Dupont-Chauvet P, Serraf A. Potts anastomosis for children with idiopathic pulmonary hypertension. Pediatr Cardiol. 2009;30(8):1143-1145.

110. Baruteau AE, Serraf A, Levy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: Long-term results. Ann Thorac Surg. 2012;94(3):817-824.
111. Apitz C, Honjo O, Humpl T, et al. Biventricular structural and functional responses to aortic constriction in a rabbit model of chronic right ventricular pressure overload. J Thorac Cardiovasc Surg. 2012;144(6):1494-1501.
112. Benden C, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: Sixteenth official pediatric lung and heart-lung transplantation report--2013; focus theme: Age. J Heart Lung Transplant. 2013;32(10):989-997.
113. Lammers AE, Burch M, Benden C, et al. Lung transplantation in children with idiopathic pulmonary arterial hypertension. Pediatr Pulmonol. 2010;45(3):263-269.
114. Schaellibaum G, Lammers AE, Faro A, et al. Bilateral lung transplantation for pediatric idiopathic pulmonary arterial hypertension: A multi-center experience. Pediatr Pulmonol. 2011;46(11):1121-1127.
115. Goldstein BS, Sweet SC, Mao J, Huddleston CB, Grady RM. Lung transplantation in children with idiopathic pulmonary arterial hypertension: An 18-year experience. J Heart Lung Transplant. 2011;30(10):1148-1152.
116. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J. 2005;26(5):858-863.
117. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D73-81.
118. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation. 2006;114(13):1417-1431.
119. Boissel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: A basis for a rational approach. Eur J Clin Pharmacol. 1992;43(3):235-244.
120. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med. 2012;31(25):2973-2984.
121. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2012;39(3):589-596.
122. Barst RJ, Chung L, Zamanian RT, Turner M, McGoon MD. Functional class improvement and 3-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL registry. Chest. 2013;144(1):160-168.
123. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol. 2002;40(4):780-788.
124. Henkens IR, Van Wolferen SA, Gan CT, et al. Relation of resting heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension. Am J Cardiol. 2009;103(10):1451-1456.
125. van Loon RL, Hoendermis ES, Duffels MG, et al. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: Does the beneficial effect persist? Am Heart J. 2007;154(4):776-782.
126. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. Int J Cardiol. 2010;142(2):159-165.
127. Douwes JM, Roofthooft MT, Bartelds B, Talsma MD, Hillege HL, Berger RM. Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension. Int J Cardiol. 2013;168(2):1370-1377.
128. Lammers AE, Adatia I, Cerro MJ, et al. Functional classification of pulmonary hypertension in children: Report from the PVRI pediatric taskforce, panama 2011. Pulm Circ. 2011;1(2):280-285.

129. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol. 2012;60(13):1192-1201.
130. Li AM, Yin J, Au JT, et al. Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. Am J Respir Crit Care Med. 2007;176(2):174-180.
131. Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease: Relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J. 2011;162(3):562-568.
132. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. Circulation. 2002;106(3):319-324.
133. Oudiz RJ, Midde R, Hovenesyan A, et al. Usefulness of right-to-left shunting and poor exercise gas exchange for predicting prognosis in patients with pulmonary arterial hypertension. Am J Cardiol. 2010;105(8):1186-1191.
134. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(3):628-634.
135. Ten Harkel AD, Takken T, Van Osch-Gevers M, Helbing WA. Normal values for cardiopulmonary exercise testing in children. Eur J Cardiovasc Prev Rehabil. 2011;18(1):48-54.
136. Yetman AT, Taylor AL, Doran A, Ivy DD. Utility of cardiopulmonary stress testing in assessing disease severity in children with pulmonary arterial hypertension. Am J Cardiol. 2005;95(5):697-699.
137. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child. 2011;96(2):141-147.
138. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102(8):865-870.
139. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation. 2010;122(2):164-172.
140. Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest. 2006;129(5):1313-1321.
141. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest. 2009;135(3):745-751.
142. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res. 2008;63(3):321-327.
143. Lammers AE, Hislop AA, Haworth SG. Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol. 2009;135(1):21-26.
144. Takatsuki S, Wagner BD, Ivy DD. B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide in pediatric patients with pulmonary arterial hypertension. Congenit Heart Dis. 2012;7(3):259-267.
145. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174(9):1034-1041.
146. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol. 2010;106(3):430-436.

147. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J. 2013;165(6):1024-1031.
148. Moledina S, Pandya B, Bartsota M, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(3):407-414.
149. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007;28(10):1250-1257.
150. Eysmann SB, Palevsky HI, Reichek N, Hackney K, Douglas PS. Two-dimensional and doppler-echocardiographic and cardiac catheterization correlates of survival in primary pulmonary hypertension. Circulation. 1989;80(2):353-360.
151. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J. 2010;36(3):549-555.
152. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010;122(2):156-163.
153. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: A reappraisal of the NIH risk stratification equation. Eur Respir J. 2010;35(5):1079-1087.
154. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660-665.
155. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: Twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation. 2005;111(24):3274-3280.
156. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2006;47(4):799-803.
157. Carmosino MJ, Friesen RH, Doran A, Ivy DD. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesth Analg. 2007;104(3):521-527.
158. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: Current insights from the magic registry. Catheter Cardiovasc Interv. 2010;76(6):865-873.
159. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MR. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. Br J Anaesth. 2007;98(5):657-661.
160. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J. In Press.
161. Ploegstra MJ, Roofthooft MTR, Douwes M, et al. The value of echocardiography in pediatric pulmonary arterial hypertension: Assessing disease severity and outcome. Am J Respir Crit Care Med. 2014;189:A3256.

5

Current clinical practice regarding the use of parental prostanoids in pediatric pulmonary arterial hypertension: how much and for how long?

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ABSTRACT

Introduction– Intravenous and subcutaneous (IV/SC) prostanoids are frequently used and considered established therapy in children with severe pulmonary arterial hypertension (PAH). However, data on dosing, timing and discontinuation of IV/SC prostanoids therapy are scarce. We report current clinical practice with regard to the use of IV/SC prostanoids in pediatric PAH and its relation with outcome.

Methods– Children who received IV/SC prostanoids were selected from a contemporary cohort (2000 - 2010) of consecutive pediatric PAH patients followed in three major referral centers: Denver, New York and the Netherlands. Timing, dosing and discontinuation of IV/SC prostanoids therapy were evaluated and its relation with lung transplantation-free survival was assessed.

Results– Ninety-eight from 275 children in the original cohort (36%) received IV/SC prostanoids. Most children started <1 year after diagnosis with IV/SC prostanoids and had severe PAH at that time: WHO functional class III-IV (76%), mean pulmonary artery pressure 65 ± 19 mmHg and indexed pulmonary vascular resistance 21.7 ± 14.4 WU.m^2. With a median follow-up of 4.2 years, 1-, 3-, 5- and 7-year transplantation-free survival was 96%, 80% 74% and 74%, respectively. In 29 children (30%) IV/SC prostanoids were discontinued and transitioned to oral/inhaled therapy: 12 children with 'near-normalization' of pulmonary hemodynamics, 17 without such normalization. Children with near-normalization showed 100% transplantation-free survival during follow-up after transition. Children without such near-normalization did less well with 2 deaths and 1 lung transplantation. In children who continued on IV/SC prostanoids therapy, a higher calculated dose during the therapy period was independently associated with more favorable transplantation-free survival.

Conclusions– In the era of PAH-targeted drugs, 36% of children with PAH were treated with IV/SC prostanoids. Most children had severe PAH and started early after diagnosis. Near-normalization of pulmonary hemodynamics during IV/SC prostanoids therapy predicted a successful transition to oral/inhaled therapy in pediatric PAH. Higher doses of IV/SC prostanoids were associated with better outcome, which appeared to be independent from disease severity and time of IV/SC prostanoids initiation.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and progressive disease of the pulmonary vasculature eventually resulting in right ventricular failure and death.[1] Three major pathways have been identified in the pathobiology of PAH: the prostacyclin, endothelin-1 and nitric oxide pathways. Various drugs that specifically target these pathways have been developed: synthetic prostacyclin(-analogues), endothelin receptor antagonists and type 5 phosphodiesterase inhibitors, respectively. Synthetic prostacyclin and its analogues, together referred to as prostanoids, take a special place in the treatment of PAH. Epoprostenol, a synthetic prostacyclin and the first PAH-targeted drug, requires continuous intravenous (IV) administration due to its very short half-life time. In following years, several chemically more stable prostacyclin analogues (beraprost, iloprost and treprostinil) have become available and allowed for subcutaneous (SC), inhaled and/or oral administration. Parental prostanoids (IV/SC) are the treatment of choice in patients with advanced PAH, both in adults and children, due to their strong vasodilating potency and well-established efficacy in patients at high risk.[2-11]

Although IV/SC prostanoids are frequently used and considered 'standard of care' in both adults and children with advanced PAH, these drugs are currently not approved for children by the European Medicines Agency or United States Food and Drug Administration. Furthermore, although guidelines provide recommendations regardingwhich patients should start with IV/SC prostanoids, it remains insufficiently clear what the optimal dose would be and whether and when IV/SC prostanoids may be discontinued and transitioned to oral/inhaled therapy.[10,11] Reported doses of IV/SC prostanoids used in pediatric PAH show a wide variation.[3,6,12,13] In a Dutch pediatric cohort, van Loon et al. reported epoprostenol doses to range from 20 to 55 ng/kg/min, while Lammers et al. reported a range from 10 to 63 ng/kg/min (mean dose 32.5 ng/kg/min) in children with idiopathic PAH in a United Kingdom cohort and Siehr et al., from a combined United States cohort, reported a range from 2 to 98 ng/kg/min (median dose 31 ng/kg/min) at one year of therapy and a range from 10 to 91 ng/kg/min (median dose 34 ng/kg/min) at three years of therapy, respectively.[6,12,13] In contrast, Barst et al. described a New York (NY) cohort and reported a mean dose of 78 ± 38 ng/kg/min after one and 116 ± 48 ng/kg/min after two years of epoprostenol therapy.[3] Data regarding IV/SC prostanoids discontinuation and transition to oral/inhaled therapy in pediatric PAH are scarce.[14,15]

In the light of the currently unsatisfactory survival in pediatric PAH and the search for optimal treatment strategies, a description and evaluation of current clinical practice of the use of IV/SC prostanoids will be helpful to assess the effect on outcome of different treatment strategies, including time of initiation, dosing and transition to oral/inhaled therapy. We brought together the contemporary consecutive pediatric PAH cohorts of three major referral centers for pediatric pulmonary hypertension (PH), as previously

described.[16] The use of uniform inclusion criteria, the inclusion of children diagnosed after 1997 and the standardized collection of data allowed for a description and evaluation of current clinical practice and outcome in pediatric PAH patients treated with IV/SC prostanoids in the current era of PAH-targeted drugs.

METHODS

Patients

For this study, all children who received IV/SC prostanoids were selected from a recently described contemporary cohort of pediatric PAH patients.[16] This cohort includes all consecutive pediatric PAH patients seen in three major referral centers for pediatric PH between 2000 and 2010: the Columbia University Medical Center, NY, NY, United States; the Children's Hospital Colorado, Aurora, Colorado, United States; and the Dutch National Referral Center for Pediatric PH, University Medical Center Groningen/Beatrix Children's Hospital, the Netherlands. In this cohort, all children had the diagnosis of PAH confirmed after 1997 during cardiac catheterization at age ≥3 months and <18 years. PAH was defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg, mean pulmonary capillary wedge pressure ≤15 mmHg and indexed pulmonary vascular resistance (PVRi) ≥3 Wood units.m^2. Children with a repaired shunt-defect had PAH confirmed >1 year after corrective surgery. Children with PH due to left heart disease, PH due to lung diseases and/or hypoxemia, or chronic thromboembolic PH are not included in this cohort. For the current study, children diagnosed with pulmonary veno-occlusive disease were excluded as such children may not respond to or even deteriorate on PAH-targeted therapies, including IV/SC prostanoids, with increased risk for developing pulmonary oedema.[17,18]

Assessments

The moment of IV/SC prostanoids initiation was defined as baseline. Patient and disease characteristics at baseline were assessed. Patient characteristics included age, sex, PAH etiology and comorbidities. Children were diagnosed according to the updated clinical classification of PH, Nice, France, 2013 and thereafter grouped into idiopathic/hereditary PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD) or associated PAH other than PAH-CHD (APAH-non-CHD).[19] Children with PAH-CHD were further classified according the Nice-CHD-classification: group 1 (Eisenmenger syndrome), group 2 (PAH with left-to-right shunts), group 3 (PAH with coincidental CHD), group 4 (post-operative PAH) or not-classifiable PAH-CHD.[19] Disease characteristics included both World Health Organization functional class (WHO-FC) and hemodynamics. Ratios of mean pulmonary-to-systemic artery pressure (mPAP/mSAP), indexed pulmonary-

to-systemic vascular resistance and indexed pulmonary-to-systemic blood flow were calculated.

Treatment definitions

The time between diagnosis and IV/SC prostanoids initiation and the duration of IV/SC prostanoids therapy were assessed. Furthermore, the duration proportional to the disease course (percentage) was calculated. Also, treatment intensity was assessed, defined as PAH-targeted monotherapy with IV/SC prostanoids if children used IV/SC prostanoids only during their disease course, or as PAH-targeted dual or triple therapy if patients also received an endothelin receptor antagonist and/or a type-5 phosphodiesterase inhibitor for at least three months or until end of follow-up.

For children who received IV/SC prostanoids for ≥3 months, we assessed 'the calculated dose during the therapy period' defined as the mean dose during the therapy period. We further determined whether IV/SC prostanoids were discontinued during the disease course and for what reasons. According to the literature as well as the treating physicians in the participating referral centers, treprostinil is dosed around 1.5 to 2.0 times higher than epoprostenol.[20-22] Therefore, in order to make doses of treprostinil equipotent and thus comparable to doses of epoprostenol, doses of treprostinil were divided by 1.75.

Statistical analyses

Data are presented as number (percentage), mean (SD) or median (interquartile range), as appropriate. One-way analysis of variance and independent samples T-test were used to compare normally distributed continuous variables. Not-normally distributed, continuous variables and ordinal variables were compared using Kruskal-Wallis or Mann Whitney U test. Chi square and Fisher's exact test were used to compare categorical variables. P-values < 0.05 were considered significant.

Outcome analyses were performed in children who received IV/SC prostanoids for ≥3 months. Lung transplantation (LTx) and death were defined as the primary endpoints in this study. Children who did not die nor undergo LTx were censored at the last follow-up visit. Transplantation-free survival was depicted from baseline using a Kaplan-Meier curve. For children in whom IV/SC prostanoids were discontinued during the disease course, transplantation-free survival was also depicted from the moment of discontinuation. Cox regression analysis was used to identify predictors for survival.

RESULTS

Current clinical practice regarding IV/SC prostanoids therapy

In total, 98 of the 275 children from the original cohort (36%) received IV/SC prostanoids during their PAH disease course and were included in this study: 11 from the Dutch cohort (originally 47 children, 23%), 31 from the Denver cohort (originally 93 children, 33%) and 56 from the New York cohort (originally 135 children, 41%).[16] Patients who received IV/SC prostanoids therapy more often had a diagnosis of IPAH/HPAH and less often a diagnosis of PAH-CHD than patients who did not receive IV/SC prostanoids. In the IV/SC prostanoids group, none of the children had Down syndrome, one child had velocardiofacial syndrome and one child had Noonan syndrome, whereas in the non-IV/SC prostanoids group significantly more associated syndromes were present, predominantly Down syndrome. Also, children initiated on IV/SC prostanoids were in higher WHO-FC and had worse hemodynamic profile compared to those in whom IV/SC prostanoids were not initiated.[16]

Patient and disease characteristics at baseline of patients who received IV/SC prostanoids therapy during their disease course are shown in Table 1. There was a female predominance and median age at diagnosis was 5.5 years. Most children had IPAH/HPAH (57%). Thirty-five children (36%) had PAH-CHD, of whom 9 had a hemodynamically relevant shunt-defect (i.e. Nice-CHD-classification groups 1 and 2) and 26 did not have such a shunt-defect (i.e. Nice-CHD-classification groups 3 and 4, or not-classifiable PAH-CHD). Seven children (7%) had APAH-non-CHD. At baseline, most children were in WHO-FC III-IV (76%), mean pulmonary artery pressure was 65 ± 19 mmHg and mean PVRi was 21.7 ± 14.4 Wood units.m^2. The majority of children (n=92, 94%) received IV epoprostenol, 28 children (29%) received IV treprostinil, 10 children (10%) received SC treprostinil and one child received IV iloprost (here the total number of children exceeds 98 since several patients had a switch from one to another IV/SC prostanoid).

Treatment characteristics are shown in Table 2. IV/SC prostanoids were initiated within one year after diagnosis in most children (77%). Twenty children (20%) received IV/SC prostanoids as PAH-targeted monotherapy during their disease course, 45 (46%) received one additional PAH-targeted drug (dual therapy) and 33 (34%) received two additional PAH-targeted drugs (triple therapy), where proportions did not differ between the center cohorts (p=0.350). Five children received IV/SC prostanoids for less than 3 months. Follow-up ended within the first three months of IV/SC prostanoids therapy in three children and two children were weaned off IV/SC prostanoids within three months after initiation (due to severe line infection in one child and per patient wish in the other child). This latter child subsequently died due to progressive right ventricular failure. In children who received IV/SC prostanoids for ≥3 months, median calculated dose during

the therapy period was 37 ng/kg/min, which ranged from 4 to 136 ng/kg/min and was highest in the NY cohort and lowest in the Dutch cohort (p<0.001).

Table 1. Patient and disease characteristics at time of IV/SC prostanoids initiation

	All patients (N=98)	
	N	Value
Age diagnosis (years)	98	5.5 (2.6, 11.6)
Female (%)	98	56 (57)
Diagnosis	98	
IPAH/HPAH		56 (57)
PAH-CHD		35 (36)
Nice-CHD 1+2		9
Nice-CHD 3		14
Nice-CHD 4		7
Unclassifiable in Nice-CHD		5
APAH-non-CHD		7 (7)
WHO-FC	84	
I		4 (5)
II		16 (19)
III		26 (31)
IV		38 (45)
mPAP (mmHg)	86	65 ± 19
mRAP (mmHg)	85	7 ± 4
PVRi (WU.m^2)	83	21.7 ± 14.4
Cardiac index (L/min/m^2)	81	3.7 ± 2.1
mPAP/mSAP	86	1.02 ± 0.31
PVR/SVR	78	1.15 ± 0.76
Qp/Qs	81	0.97 ± 1.28

Data presented as median (interquartile range), number (percentage) or mean ± SD.
APAH-non-CHD, associated pulmonary arterial hypertension other than congenital heart disease; IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; mPAP/mSAP, mean pulmonary-to-systemic artery pressure ratio; mRAP, mean right atrial pressure; Nice-CHD, Nice congenital heart disease classification; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PVRi, indexed pulmonary vascular resistance; PVR/SVR, indexed pulmonary-to-systemic vascular resistance ratio; Qp/Qs, indexed pulmonary-to-systemic blood flow ratio; WHO-FC, World Health Organization functional class; WU, Wood units.

Table 2. Treatment characteristics

	All patients (N=98)	Dutch cohort (n=11)	Denver cohort (n=31)	NY cohort (n=56)	P-value
Time between diagnosis and IV/SC prostanoid initiation (months)	0.7 (0.0, 8.5)	0.5 (0.0, 13.2)	0.8 (0.2, 12.0)	0.8 (0.0, 8.5)	0.518
Start <1 year after diagnosis	75 (77)	8 (73)	23 (74)	44 (79)	0.831
% of disease course on IV/SC therapy	82 (45, 99)	96 (32, 100)	68 (30, 98)	86 (54, 100)	0.262
Calculated dose during therapy period*	37 (20, 63; 4 – 136)	17 (15, 20; 9 – 25)	31 (18, 42; 9 – 98)	54 (30, 74; 4 – 136)	<0.001
Treatment intensity:					0.350
PAH-targeted monotherapy	20 (20)	3 (27)	3 (10)	14 (25)	
PAH-targeted dual therapy	45 (46)	6 (55)	16 (52)	23 (41)	
PAH-targeted triple therapy	33 (34)	2 (18)	12 (39)	19 (34)	

Data presented as median (interquartile range) or number (percentage). For calculated dose during the therapy period, range is also shown. * For children who received IV/SC prostanoids for ≥3 months (N=93, including 9 Dutch, 29 Denver and 55 NY patients).
IV, intravenous; NY, New York; PAH, pulmonary arterial hypertension; SC, subcutaneous.

During their disease course, IV/SC prostanoids were discontinued in 29 children (30%). Patient and disease characteristics at baseline did not differ between children in whom IV/SC prostanoids were discontinued and children in whom IV/SC prostanoids were continued, except for a lower mean right atrial pressure (mRAP) in the first group (6 ± 4 mmHg vs. 8 ± 4 mmHg, p=0.034). Children in whom IV/SC prostanoids were discontinued tended to have started with IV/SC prostanoids more frequently within the first year after diagnosis (90% vs. 70%, p=0.064) and had a lower calculated dose during the therapy period (median 28 vs. 43 ng/kg/min, p=0.015). Treatment intensity, i.e. PAH-targeted mono-, dual or triple therapy, did not differ between these two groups.

Of the 93 children who received IV/SC prostanoids for ≥3 months, 18 died and 7 underwent LTx during a median follow-up of 4.2 (IQR 1.8, 8.0) years (Figure 1A). Causes of death were progressive right ventricular failure (n=9), lung bleeding/hemoptysis (n=4), pulmonary hypertensive crises (n=2), non-pulmonary bleedings (n=2) and liver failure after liver transplant for portopulmonary PAH (n=1).

Children with transition to oral/inhaled therapy

In 2 children from the Netherlands (18%), 11 from Denver (35%) and 16 from NY (29%), IV/SC prostanoids were discontinued and these children were transitioned to oral and/or inhaled PAH-targeted therapy (n=28) or to calcium channel blocker monotherapy (n=1). In 21 children, of which 8 had IV/SC prostanoids initiated before the year 2001, the treating physician at the referral center decided for transition because he/she expected the child to do well on oral/inhaled therapy. In 5 children IV/SC prostanoids had to be

discontinued due to side-effects (weight loss and diarrhoea, n=1) or administration-related complications (line infection/sepsis [n=3] or infusion disruption [n=1]). In 3 other children, IV/SC prostanoids were discontinued per patient wish or due to non-compliance.

At time of discontinuation, 12 of the 29 children (41%) had near-normalization of pulmonary hemodynamics, which was arbitrarily defined as mPAP <30 mmHg and PVRi <6.0 Wood units.m^2. This was not the case in the remaining 17 children. Patient, disease and treatment characteristics, as shown in Tables 1 and 2, did not differ between these two groups. At the moment of discontinuation, all children with near-normalization of pulmonary hemodynamics were in WHO-FC I-II, median mPAP was 23 (IQR 20, 26) mmHg and median PVRi 2.9 (IQR 1.8, 4.2) Wood units.m^2. All these children had an uneventful follow-up: IV/SC prostanoids were not restarted in any of the children neither did any of these children die nor undergo LTx during the study period (Figure 1B). Of the children without near-normalization of pulmonary hemodynamics, most (88%) were in WHO-FC I-II (missing in 1 child) at moment of discontinuation, whereas median mPAP was 53 (IQR 40, 65) mmHg (missing in 4 children) and PVRi was 9.3 (IQR 8.2, 19.8) Wood units. m^2 (missing in 6 children). Of these 17 children, 2 died and one underwent LTx during the study period (Figure 1B). IV/SC prostanoids therapy was restarted in four children due to clinical deterioration, including one of the children who died and the child who underwent LTx.

Outcome of children with IV/SC prostanoids continuation

In 64 children IV/SC prostanoids were continued during their disease course (Dutch cohort n=7, Denver cohort n=18 and NY cohort n=39). One-, 3-, 5- and 7-year survival rates were 93%, 72%, 64% and 64%, respectively. In this group we performed Cox regression analysis to identify predictors of survival for children on IV/SC prostanoids therapy. In univariate analysis, older age at diagnosis and higher mRAP, PVRi and mPAP/mSAP were associated with worse transplantation-free survival (Table 3). A higher calculated dose during the therapy period was associated with better outcome. This association was maintained when corrected for the variables significantly associated with lung transplantation-free survival in univariate analysis and also when corrected for all variables included in univariate analysis. In this study, sex, the presence of a hemodynamically relevant shunt-defect, WHO-FC, cardiac index and the time between diagnosis and IV/SC prostanoids initiation were not associated with transplantation-free survival.

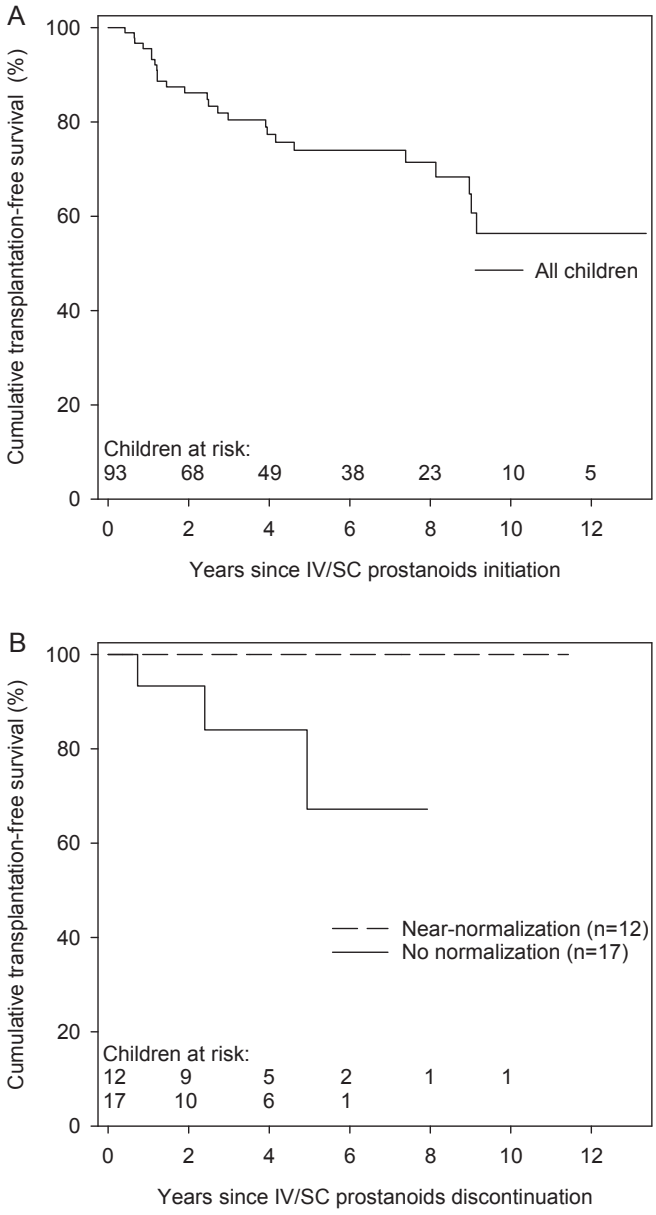

Figure 1. Transplantation-free survival of children who received IV/SC prostanoids
A. From IV/SC prostanoids initiation for all children treated with IV/SC prostanoids ≥3 months during their disease course. One-, 3-, 5- and 7-year survival rates were 96%, 80%, 74% and 74%, respectively.
B.From the moment of IV/SC prostanoids discontinuation of children with near-normalization of pulmonary hemodynamics (n=12) and children without such normalization (n=17). One-, 3-, and 5-year survival rates after discontinuation were 100%, 100% and 100% for the first group and 93%, 84% and 67% for the latter group, respectively.

Table 3. Predictors for transplantation-free survival in children with IV/SC prostanoids continuation

	Univariate analysis	
	Hazard ratio (95% CI)	P-value
Age diagnosis	1.158 (1.057 – 1.268)	0.002
Female sex	1.428 (0.605 – 3.374)	0.416
Hemodynamically relevant shunt-defect	0.439 (0.059 – 3.287)	0.423
WHO-FC III-IV	0. 873 (0.313 – 2.434)	0.795
mRAP	1.138 (1.021 – 1.268)	0.020
PVRi	1.040 (1.014 – 1.067)	0.003
Cardiac index	0.861 (0.662 – 1.121)	0.266
mPAP/mSAP	4.263 (0.987 – 18.410)	0.052
Calculated dose during the therapy period (per 10 ng/kg/min)	0.737 (0.612 – 0.889)	0.001
Time between diagnosis and initiation of IV/SC prostanoids	1.163 (0.876 – 1.544)	0.297

Data presented as hazard ratios with 95% confidence intervals.
CI, confidence interval; IV, intravenous; mPAP/mSAP, mean pulmonary-to-systemic artery pressure ratio; mRAP, mean right atrial pressure; PVRi, indexed pulmonary vascular resistance; SC, subcutaneous; WHO-FC, World Health Organization functional class.

DISCUSSION

Before the 2000s, IV/SC prostanoids were the only available PAH-targeted drugs. From 2001 onwards, oral and inhaled PAH-targeted drugs were introduced and allowed for oral and inhaled treatments for patients with lower risk PAH.[10,11] Current guidelines recommend to start oral PAH-targeted therapy in children with PAH at low risk, but to initiate IV/SC prostanoids without delay in patients with PAH at high risk and to escalate therapy eventually to IV/SC prostanoids if there is an inadequate clinical response.[10,11] In the current contemporary multicenter cohort, a little more than one-third (36%) of the children received IV/SC prostanoids during the course of their disease, which is in the range of previous current era reports.[12,16,23,24] Parental prostanoids were given often in combination with other PAH-targeted drugs. In the current study, children most frequently started with IV/SC prostanoids already early after diagnosis and had severe PAH at that time. As reported previously, children who received IV/SC prostanoids had a diagnosis of IPAH/HPAH more frequently, less associated syndromes, higher WHO-FC and worse hemodynamics compared to children who did not receive IV/SC prostanoids during their disease course.[16] In this subgroup of high risk patients on IV/SC prostanoids therapy, transplantation-free survival was unsatisfactory, with a 5-year survival rate of 74%, which is on the lower range of reported survival rates in the current era of PAH-targeted drugs and worse compared to the total original cohort (5-year survival rate

81%).[16,23,25,26] Thus, children who receive IV/SC prostanoids form a selective group of pediatric PAH patients with severe disease and, although IV/SC prostanoids do improve survival compared to conventional therapies, outcome remains unfavorable.[3,27]

In the current study, IV/SC prostanoids were discontinued in approximately one-third of the children, who were all transitioned to an oral/inhaled treatment regimen. Melnick et al. reported uneventful transition to non-IV/SC therapy in 13 out of 104 children who received IV/SC prostanoids with IPAH or familial PAH and who all were in WHO-FC I-II and had a mPAP of <35 mmHg.[15] Ivy et al. previously reported uneventful transition in 3 children, with normal or near-normal pulmonary hemodynamics, out of 8 children with IPAH also receiving the endothelin receptor antagonist bosentan.[14] In both studies children did well after transition, meaning no restarts of IV/SC prostanoids, deaths or LTx.[14,15] However, follow-up was short: 1 to 6 years for Melnick et al. and <1 year for Ivy et al. Based on these limited data no well-founded recommendations can be made regarding the transition of parental prostanoids to oral/inhaled therapy in children with PAH. In the current study, we were able to evaluate transition to oral/inhaled therapy in 29 children with markedly longer follow-up after IV/SC prostanoids discontinuation allowing for more robust evaluation of medium to long term outcome after parental prostanoids discontinuation. Children with near-normalization of pulmonary hemodynamics showed excellent longer-term outcome after discontinuation. Therefore, this study suggests that WHO-FC I-II associated with near-normalization of pulmonary hemodynamics during IV/SC prostanoids therapy predicts successful transition to oral/inhaled therapy, also on the long-term and thus could be considered in such children. On the other hand, children without such normalization appeared to do significantly less well with poor survival, despite restart of IV/SC prostanoids, and therefore transition to oral/inhaled therapy should not be advocated in these children. The use of strict hemodynamic criteria, i.e. mPAP <30 mmHg and PVRi <6.0 Wood units.m^2, appeared to adequately differentiate between children who did well on oral/inhaled therapy and children who did not. Importantly, the majority of children without near-normalization of pulmonary hemodynamics, in whom IV/SC prostanoids were still discontinued, was in WHO-FC I-II at time of discontinuation, indicating that decisions regarding transition to oral/inhaled therapy should not be based on favorable WHO-FC alone. Therefore, our study highlights the important role of pulmonary hemodynamics in this decision, which may outweigh the risks of cardiac catheterization related complications in patients in low WHO-FC.[28,29]

Reported doses of IV/SC prostanoids used in pediatric PAH differ significantly.[3,6,12,13] This study confirms that doses of IV/SC prostanoids used in current clinical practice vary highly and that the participating centers in this study used different dosing strategies for parental prostanoids. This variation is also reflected by the current adult and pediatric guidelines. The adult guidelines state that the optimal dose varies between

individual patients and lies between 20 and 40 ng/kg/min for epoprostenol in most patients, between 20 and 80 ng/kg/min for SC treprostinil and 2 to 3 times higher than epoprostenol for IV treprostinil.[11] Pediatric guidelines have stated that the effective dose of epoprostenol is often higher in children than in adults with a broad range from 40 to >150 ng/kg/min and an average dose of ≈80 ng/kg/min.[10] For IV and SC treprostinil, a stable dose is stated to be usually between 50 and 80 ng/kg/min.[10] However, no data to support such statements are currently available. Importantly, we observed for the first time that a higher calculated dose during the therapy period was associated with better outcome in children who remained on IV/SC prostanoids, which appeared to be independent from patient characteristics, disease severity and time from diagnosis to initiation of IV/SC prostanoids therapy. These findings suggest that higher doses of IV/SC prostanoids are associated with a beneficial effect on prognosis. Given the unfavorable outcome in pediatric PAH and the currently limited data regarding the 'when, how and for how long' of IV/SC prostanoids in the treatment of pediatric PAH, these unique findings provide valuable new insights on this issue.

An important limitation of IV/SC prostanoids is that these are associated with significant administration-related complications or side-effects including line infections, bacteremia and sepsis.[30-32] It also poses a risk for line thrombosis, which could lead to systemic embolic complications in patients with PAH-CHD and a right-to-left shunt. Furthermore, a sudden halt of IV epoprostenol therapy may lead to possible fatal rebound PH. For SC therapy, pain and infection of the injection site are common.[4] IV/SC prostanoids had to be discontinued in 5 children (5% of the cohort) due to such complications or severe side-effects. None of the children died due to administration-related complications or side-effects, or accidental sudden halt of infusion and rebound PH.

This description of current clinical practice provides valuable information regarding the place of IV/SC prostanoids in the treatment of pediatric PAH in the current era of PAH-targeted drugs. A unique collaboration between three major referral centers for pediatric PAH and the use of uniform inclusion criteria has led to one of the largest pediatric PAH cohorts to date and provided the opportunity to specifically study the subgroup of children treated with IV/SC prostanoids. Furthermore, different dosing strategies between the participating centers allowed for evaluating the effect of dosing on outcome. Its retrospective character and relatively small sample size limit this study and hamper multivariate analyses. Therefore, conclusions regarding a causative relation between higher doses, timing of initiation of IV/SC prostanoids and outcome cannot be drawn. Prospective studies are warranted on this issue, which may be provided by newly designed multicenter and/or multinational collaborations and so-called 'smart-design' clinical trials. More detailed data regarding the occurrence of side-effects and adverse drug reactions would have been a valuable addition to this study but were not available.

CONCLUSIONS

In the current era of PAH-targeted drugs, a substantial proportion of children with PAH received IV/SC prostanoids during their disease course. These children predominantly had advanced disease and started IV/SC prostanoids therapy within a year after diagnosis. Also, they frequently received additional PAH-targeted drugs. Near-normalization of pulmonary hemodynamics while on IV/SC prostanoids therapy predicted a successful transition to oral/inhaled therapy in pediatric PAH. If there is no such normalization, even when the child is in WHO-FC I-II, transition to oral/inhaled therapy should not be considered. In children on continuous IV/SC prostanoids therapy, higher doses may have beneficial effects on outcome, independent from disease severity or time of IV/SC prostanoids initiation.

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REFERENCES

1. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
2. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296-301.
3. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
4. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165(6):800-804.
5. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660-665.
6. Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. Heart. 2007;93(6):739-743.
7. Nakayama T, Shimada H, Takatsuki S, et al. Efficacy and limitations of continuous intravenous epoprostenol therapy for idiopathic pulmonary arterial hypertension in japanese children. Circ J. 2007;71(11):1785-1790.
8. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr. 2011;158(4):584-588.
9. Benza RL, Tapson VF, Gomberg-Maitland M, Poms A, Barst RJ, McLaughlin VV. One-year experience with intravenous treprostinil for pulmonary arterial hypertension. J Heart Lung Transplant. 2013;32(9):889-896.
10. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the american heart association and american thoracic society. Circulation. 2015;132(21):2037-2099.
11. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS): Endorsed by: Association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
12. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
13. Siehr SL, Ivy DD, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: Long-term hemodynamics. J Heart Lung Transplant. 2013;32(5):546-552.
14. Ivy DD, Doran A, Claussen L, Bingaman D, Yetman A. Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. Am J Cardiol. 2004;93(7):943-946.
15. Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. Am J Cardiol. 2010;105(10):1485-1489.

16. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
17. Montani D, Achouh L, Dorfmuller P, et al. Pulmonary veno-occlusive disease: Clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine (Baltimore). 2008;87(4):220-233.
18. Huertas A, Girerd B, Dorfmuller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: Advances in clinical management and treatments. Expert Rev Respir Med. 2011;5(2):217-29; quiz 230-1.
19. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
20. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005;172(12):1586-1589.
21. Rubenfire M, McLaughlin VV, Allen RP, et al. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: A controlled trial. Chest. 2007;132(3):757-763.
22. Ivy DD, Claussen L, Doran A. Transition of stable pediatric patients with pulmonary arterial hypertension from intravenous epoprostenol to intravenous treprostinil. Am J Cardiol. 2007;99(5):696-698.
23. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
24. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.
25. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
26. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
27. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. results from a national prospective registry. Ann Intern Med. 1991;115(5):343-349.
28. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: Current insights from the magic registry. Catheter Cardiovasc Interv. 2010;76(6):865-873.
29. Beghetti M, Schulze-Neick I, Berger RM, et al. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the global TOPP registry (tracking outcomes and practice in paediatric pulmonary hypertension). Int J Cardiol. 2016;203:325-330.
30. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132(6):425-434.
31. Dickinson MG, Scholvinck EH, Boonstra A, Vonk-Noordegraaf A, Snijder RJ, Berger RM. Low complication rates with totally implantable access port use in epoprostenol treatment of pulmonary hypertension. J Heart Lung Transplant. 2009;28(3):273-279.
32. Barst R. How has epoprostenol changed the outcome for patients with pulmonary arterial hypertension? Int J Clin Pract Suppl. 2010;(168):23-32. doi(168):23-32.

6

Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis

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ABSTRACT

Background– Despite the introduction of targeted therapies in pediatric pulmonary arterial hypertension (PAH), prognosis remains poor. For the definition of treatment strategies and guidelines, there is a high need for an evidence-based recapitulation of prognostic factors. The aim of this study was to identify and evaluate prognostic factors in pediatric PAH by a systematic review of the literature and to summarize the prognostic value of currently reported prognostic factors using meta-analysis.

Methods and Results– Medline, EMBASE and Cochrane Library were searched on April 1st 2014 to identify original studies that described predictors of mortality or lung transplantation exclusively in children with PAH. 1053 citations were identified, of which 25 were included for further analysis. Hazard ratios (HR) and 95% confidence intervals were extracted from the papers. For variables studied in at least three non-overlapping cohorts, a combined HR was calculated using random-effects meta-analysis. WHO functional class (WHO-FC, HR 2.7), (N-terminal pro) brain natriuretic peptide ([NT-pro] BNP, HR 3.2), mean right atrial pressure (mRAP, HR 1.1), cardiac index (HR 0.7), indexed pulmonary vascular resistance (PVRi, HR 1.3) and acute vasodilator response (HR 0.3) were identified as significant prognostic factors ($p \leq 0.001$).

Conclusions– This systematic review combined with separate meta-analyses shows that WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response are consistently reported prognostic factors for outcome in pediatric PAH. These variables are useful clinical tools to assess prognosis and should be incorporated in treatment strategies and guidelines for children with PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe progressive disease of the pulmonary vasculature, leading to increased pulmonary vascular resistance (PVR), right ventricular (RV) failure and death.[1] Since the recent introduction of specific PAH-targeted drugs, quality of life and survival in both children and adults have improved, but remain unsatisfactory.[2-4]

For clinical decision-making in the treatment of these patients, it is important to be able to predict survival using prognostic factors.[5] In adults with idiopathic PAH, various prognostic factors have been identified and reviewed.[6,7] Although data in children are limited, several pediatric studies have recently reported on survival and prognostic factors. These data, however, are mostly derived from relatively small patient series and contradictory findings have been reported. It is unclear whether contradictions that have emerged from recent pediatric studies can be explained by differences in study populations, different treatment strategies or by insufficient power of the individual studies due to small sample sizes.

There is a high clinical need to improve treatment strategies and to define guidelines for the management of children with PAH. Therefore, it is of great importance to identify, appraise, synthesize and combine the currently available data on prognostic factors in pediatric PAH. This will help in defining current evidence and in developing supportive guidelines for the management of infants and children with PAH. Hence, the aim of this study was to identify and evaluate prognostic factors in pediatric PAH, by a systematic review of the literature and to subsequently summarize the prognostic value of currently reported prognostic factors in children with PAH using meta-analysis.

METHODS

Literature search

Medline, EMBASE and Cochrane Library were searched on April 1st 2014. The initial literature search focused on the overlapping part of three elements: (1) PAH, (2) children and (3) survival. To achieve this, a search string was composed and adapted to the three literature databases (supplementary file, Table A.1). The keyword 'primary pulmonary hypertension' was also included, as this term was previously used for idiopathic PAH (IPAH). In contrast, the formerly used term 'secondary pulmonary hypertension' for PH other than IPAH was not included because this group also comprised forms of PH with different etiologies and disease mechanisms than PAH. The search was limited to human studies and English language. The reference lists of all primary identified articles were hand searched for additional relevant publications.

Study selection

Titles and abstracts were screened by two independent reviewers (M.J.P and W.M.H.Z., investigators) to identify studies that described predictors of mortality in children with PAH. Eligible studies were required to report at least (1) data on mortality in pediatric PAH and (2) variables studied in relation to mortality. Studies were considered ineligible if they were animal studies or review articles, were not limited to children or when no survival analysis (Cox regression analysis or Kaplan-Meier survival analysis) was performed. All remaining studies underwent full-text review, with a targeted focus on the study population and survival analysis details. Studies were excluded when >20% of the study population did not meet the current PAH definition according to the updated Nice classification.[8] Studies using endpoints other than death or death + lung transplantation were also excluded. Any disagreements between the reviewers were resolved by discussion leading to consensus or by consulting a third-party arbitrator (H.L.H., epidemiologist/statistical consultant).

Data extraction

Of all studied variables, hazard ratios (HR) and 95% confidence intervals (CI) derived from univariable Cox regression analysis were extracted from the papers. When the CI was not reported, the P-value was used to estimate the CI.[9] When only Kaplan-Meier analysis was performed to assess a variable's relation with survival, HR and CI were estimated using Parmar's survival curve method, on the condition that picture quality and description of patient numbers were sufficient.[10] When individual patient data were provided in the paper in the absence of a reported HR, the HR and CI were calculated using Cox regression analysis rather than estimated from the survival curve. When the HR was described for death and death + lung transplantation, the HR for death was extracted. When analyses were performed for characteristics at different baseline moments (e.g. both time of diagnosis and study enrollment), the baseline with least missing values was used.

Data synthesis

Multiple separate random-effects meta-analyses were conducted to calculate combined HRs for sufficiently studied candidate prognostic factors. The following methodological considerations were taken into account: (1) patient-overlap between studies, (2) sufficiency of number of combinable studies, (3) differences in how the HR was calculated and (4) potential between-study heterogeneity.

Patient-overlap between studies is likely to exist, since most studies on pediatric PAH are performed in a limited number of centers. When a variable was studied and reported more than once by the same center with overlapping inclusion periods, only the HR from the largest study was included in the meta-analysis. In case of exactly matching patient numbers, the most recent study was included. HRs from studies that combined previously published cohorts in a new individual patient data level analysis were excluded,

unless a HR was not available from the original cohort studies. The HRs of all excluded studies were still displayed in the meta-analysis forest plots in a different color to retain overview of the entirety and consistency of the available data.

Meta-analysis was only considered appropriate when a candidate prognostic factor was studied in at least three non-overlapping cohorts. When meta-analysis was not appropriate, results were summarized in tabular form.

Differences in how the HR was calculated, such as variation in the number of units change used for HR calculation (e.g. when one study reported the HR per 1 mmHg pressure change while another reported the HR per 5 mmHg change), were addressed by recalculating the HRs using a uniform clinically applicable number of units change. HRs of dichotomized continuous variables (i.e. when patients with high values were compared to patients with low values), could not be recalculated and were left unadjusted. HRs based on dichotomized variables were not combined with HRs based on continuous variables, but were displayed separately. The choice of including HRs based on dichotomized or continuous variables in meta-analyses depended on how often the methods were applied: studies with the least applied method were excluded from the meta-analysis but were still displayed in the forest plot in a different color to retain overview of the entirety and consistency of the available data.

Heterogeneity was assessed using both Cochran's Q-test and the I^2 quantity. In view of the small number of studies to be compared, a Q-test p-value <0.10 or an I^2 quantity >50% were considered indicative of substantial heterogeneity. In the case of a statistically significant combined weighted HR in combination with substantial evidence for heterogeneity, the methodological characteristics and study populations were compared and exploratory subgroup analysis and meta-regression were conducted to identify potential causes of heterogeneity. Analyses were performed using STATA 11.0 (STATA corp., College Station, Texas, USA).

RESULTS

Identified studies

In total, 1053 citations were identified (Figure 1). With screening titles and abstracts, 989 citations were excluded, leaving 64 articles for full-text review (references are listed in the supplementary file). Screening full articles identified 27 articles that described prognostic factors for survival exclusively in pediatric PAH (supplementary file, Table A.2). Exclusion reasons per publication are shown in Table A.3. Additionally, two primarily identified studies were excluded from further data analysis because of inconsistency in data reporting within the paper[11], and because of demonstrable 100% patient-overlap with a previously published report.[12] The main characteristics of the remaining 25 studies are outlined in Table 1.

Table 1. Study Characteristics

Study [Reference]	Patient number	Study baseline	Type of survival analysis	Endpoint	IPAH/HPAH/Primary PH(%)	APAH-CHD (%)	APAH-non-CHD (%)	Other types of PH (%)	Sex male (%)	Age (yrs)	WHO-FC	NT-proBNP (pg/mL)	BNP (pg/mL)	mRAP (mmHg)	mPAP (mmHg)	Cardiac Index (L/min/m^2)	PVRi (WU*m^2)	Acute vasodilator response[e] (%)
Sandoval 1995 [14]	18	D	Cox	Dt	100	0	0	0	39	9.9	2.8			5.4[d]	66.0[d]	4.1[d]	18.4[d]	59[d]
Clabby 1997 [26]	50	D	Cox	Dt	30	70	0	0	35	8.3				6.1	62.0	3.6	22.0	
Barst 1999 [15]	77	D	Cox	Dt	100	0	0	0	35	7.0	2.9			5.0	65.0	3.1	22.0	42[d]
Nakayama 2007 [24]	31	T	KM	Dt/Ltx	100	0	0	0	52	10.7	3.3		511	9.2[d]	84.1[d]	2.3[d]	32.4	
Van Albada 2008 [22]	29	P	KM[a]	Dt	62	38	0	0	38	7.0[c]		1065						
Bernus 2009 [23]	78	O	KM	Dt	33	53	8	6	46	9.3[c]			36[c]	6.0[c,d]	38.0[c,d]	3.5[c,d]	6.5[c,d]	
Haworth 2009 [49]	216	P	KM	Dt	28	48	4	20	46	7.7	3.1				52.4[d]		17.4[d]	
Lammers 2009 [25]	50	P	KM	Dt/Ltx	54	34	2	10	64	8.4	2.7		144	9.1[d]	62.4[d]		19.5[d]	
Van Loon 2010 [3]	52	D	Cox	Dt	56	44	0	0	37	3.1[c]	2.9	501		7.0	55.0	2.8	20.5	15
Lammers 2010 [27]	47	O	Cox	Dt/Ltx	45	45	0	10	57	11.4	2.7			8.3	58.4		22.1	
Alkon 2010 [50]	47	O	Cox	Dt/Ltx	36	64	0	0	32	5.5[c]	1.8							
Moledina 2010 [17]	64	P	Cox	Dt	100	0	0	0	37	6.5[c]	3.1			7.1[d]	58.0[d]	2.9[d]	19.7[d]	9[d]
Ivy 2010 [21]	86	T	Cox	Dt	42	56	2	0	43	11.0	2.3			7.0[d]	63.0[d]	3.6[d]	20.0[d]	
Hislop 2011 [19]	101	T	KM	Dt	42	58	0	0	42	9.7	2.8			7.6[d]	56.4[d]		21.1[d]	
Moledina 2011 [20]	31	O	Cox	Dt	39	45	0	16	42	10.3	2.6			6.0[c,d]	42.0[c,d]		13.2[c,d]	
Van Loon 2011 [51]	154	D	KM	Dt	23	72	5	0	49	2.2[c]	2.5[d]			7.0[d]	51.0[d]	2.7[d]	17.8[d]	
Barst 2012 [16]	216	E	Cox	Dt	56	36	8	0	36	15.0[c]	2.1			7.0	56.0	3.7	17.0	27[d]

Table 1. Study Characteristics (continued)

Study [Reference]	Patient number	Study baseline	Type of survival analysis	Endpoint	IPAH/HPAH/Primary PH(%)	APAH-CHD (%)	APAH-non-CHD (%)	Other types of PH (%)	Sex male (%)	Age (yrs)	WHO-FC	NT-proBNP (pg/mL)	BNP (pg/mL)	mRAP (mmHg)	mPAP (mmHg)	Cardiac Index (L/min/m^2)	PVRi (WU*m^2)	Acute vasodilator response[e] (%)
Chida 2012 [52]	54	O	Cox	Dt	100	0	0	0	44	8.5			57[c,d]	6.8[d]	64.3[d]	3.2[d]	19.1[d]	
Apitz 2012 [53]	43	D	KM	Dt/Ltx	100	0	0	0	44	10.4	2.4				67.1	3.0	23.5	49
Douwes 2013 [18]	52	P	Cox	Dt/Ltx	64	36	0	0	40	7.1[c]	2.8			6.0[c]	51.0	2.8[c]	14.6[c]	
Moledina 2013 [41]	100	D	Cox	Dt/Ltx	60	22	?[b]	?[b]	39	10.4[c]	2.3							
Kassem 2013 [54]	54	E	KM	Dt/Ltx	33	67	0	0	35	8.0							18.5	
Wagner 2013 [13]	83	O	Cox	Dt	43	57	0	0	51	8.3[c]				6.0[c,d]	40.0[c,d]	4.0[c,d]	7.9[c,d]	
Chida 2014 [55]	59	O	Cox	Dt	100	0	0	0	44	11.3	3.0	1669		7.3	65.5	3.1	21.3	
Zijlstra 2014 [4]	275	D	Cox	Dt/Ltx	52	42	6	0	41	6.4[c]	2.6	708[d]	81[d]	6.0[d]	55.0	3.6[d]	15.8	25[d]

Data presented as percentage or mean, unless stated otherwise. PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; IPAH = idiopathic PAH; APAH = associated PAH; CHD = congenital heart disease; WHO-FC = WHO functional class, NT-proBNP = N-terminal-pro brain natriuretic peptide; BNP = brain natriuretic peptide; mRAP = mean right atrial pressure; mPAP = mean pulmonary artery pressure; PVRi = indexed pulmonary vascular resistance; D = diagnosis; T = treatment start; P = presentation; E = enrollment; O = other, Cox = Cox regression analysis; KM = Kaplan-Meier analysis; Dt = death; Dt/Ltx = death or lung-transplantation.

[a] Also individual patient data available in paper, allowing for hazard ratio calculation. [b] The diagnosis of 18% of the patients in this study was described as 'miscellaneous causes of PH', which could be interpreted as either APAH-non-CHD or other types of PH. [c] Median (mean not reported in paper). [d] Calculated within a subgroup of the cohort. [e] Vasodilators and definitions of a favorable response differed throughout the studies.

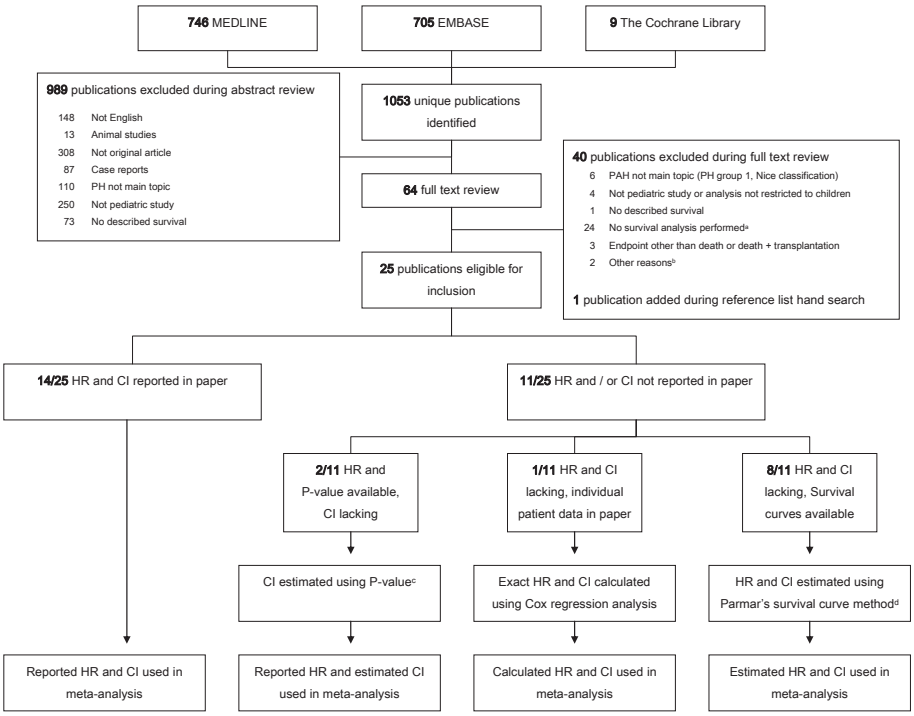

Figure 1. Flow chart showing study selection and data extraction

[a] Survival analysis in which a candidate prognostic factor is evaluated using Cox regression analysis or Kaplan Meier analysis (not: comparison of treatment group survival). [b] Other reasons included: inconsistency in data reporting within the paper and demonstrable 100% patient overlap with another included paper. [c] See Altman et al. 2011.[9] [d] See Parmar et al. 1998.[10]

PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; HR = hazard ratio; CI = 95% confidence interval.

Identified candidate prognostic factors

Table 2 summarizes a total of 40 variables that have been shown to be significantly related to survival in one or more studies. The availability of HRs (either directly reported or indirectly calculable) is also shown in Table 2. For 10 of the 40 identified variables, there were HRs available from at least three non-overlapping cohorts. For these 10 candidate prognostic factors, a combined HR and accompanying P-value could be calculated using meta-analysis (Table 3). The corresponding forest plots are displayed in Figures 2-4. The meta-analysis results of the 10 candidate prognostic factors are detailed below.

Age was investigated in 10 studies, with HRs available from 6/10 studies (Table 2). One of these 6 was omitted from meta-analysis to prevent duplicate patient inclusion (Figure 2).[13] Combining the remaining 5 non-overlapping cohorts representing 426 patients yielded a HR (CI) of 1.01 (0.92-1.10) per year increase (Figure 2, p=0.866), indicating no significant association with survival. North-American studies (Sandoval, Barst 1999,

Table 2. Variables associated with survival, per study

	Sandoval 1995 [14]	Clabby 1997 [26]	Barst 1999 [15]	Nakayama 2007 [24]	Van Albada 2008 [22]	Bernus 2009 [23]	Haworth 2009 [49]	Lammers 2009 [25]	Van Loon 2010 [3]	Lammers 2010 [27]	Alkon 2010 [50]	Moledina 2010 [17]	Ivy 2010 [21]	Hislop 2011 [19]	Moledina 2011 [20]	Van Loon 2011 [51]	Barst 2012 [16]	Chida 2012 [52]	Apitz 2012 [53]	Douwes 2013 [18]	Moledina 2013 [41]	Kassem 2013 [54]	Wagner 2013 [13]	Chida 2014 [55]	Zijlstra 2014 [4]	N times studied	N times significant	N extractable HRs[a]	N HRs from non-overlapping cohorts
Demographic																													
Age	×	✖	↘						✖			×	✖				×						↘		✖	10	2	6	5
Sex	×	✖	↘						✖			↘	✖				×	×					✖		✖	10	2	5	5
Clinical																													
Diagnosis		✖					×		×				✖			↘	×			×					↘	9	2	7	3
WHO-FC	×								↘	↘		↘	↘		×		×			↘			↘		↘	11	8	10	4
6MWT									✖	↘					✖						✖		✖		✖	6	1	2	1
Heart rate	×								✖											↘	↘		✖			5	2	2	2
Systolic RR									↘								×						✖		↘	4	2	3	2
Diastolic RR									↘																↘	2	2	2	1
Height												↘					×						✖		✖	4	1	2	2
Weight									✖			↘					×						✖			4	1	2	2
BSA																							↘			1	1	1	1
Heart rate variability										↘																1	1	1	1
peak VO2																							↘			1	1	1	1
VE/VCO2 slope																							↘			1	1	1	1
BMPR2 mutation																		↘								1	1	1	
Biochemical																													
(NT-pro)BNP				↘	↘	↘			↘								↘						✖		↘	9	8	8	4
Uric Acid					↘				↘														↘			3	3	3	2
Hb		✖																					↘			2	1	1	1

Table 2. Variables associated with survival, per study (continued)

	Sandoval 1995 [14]	Clabby 1997 [26]	Barst 1999 [15]	Nakayama 2007 [24]	Van Albada 2008 [22]	Bernus 2009 [23]	Haworth 2009 [49]	Lammers 2009 [25]	Van Loon 2010 [3]	Lammers 2010 [27]	Alkon 2010 [50]	Moledina 2010 [17]	Ivy 2010 [21]	Hislop 2011 [19]	Moledina 2011 [20]	Van Loon 2011 [51]	Barst 2012 [16]	Chida 2012 [52]	Apitz 2012 [53]	Douwes 2013 [18]	Moledina 2013 [41]	Kassem 2013 [54]	Wagner 2013 [13]	Chida 2014 [55]	Zijlstra 2014 [4]	N times studied	N times significant	N extractable HRs[a]	N HRs from non-overlapping cohorts
Norepinephrine					✔																					1	1	1	1
Apo-A1																							✔			1	1	1	1
TIMP-1																							✔			1	1	1	1
sST2																								✔		1	1	1	1
Hemodynamic																													
mRAP	✘	✔	✔						✘	✘		✘	✘										✘		✔	9	3	6	3
mPAP	✘	✔	✔						✘	✘		✘	✘							✘	✘		✔		✘	11	3	7	4
mPAP/mSAP		✘							✔								✔			✔			✘		✔	6	4	4	2
PVRi	✘	✔	✔						✘	✔		✘	✔		✘		✔			✘			✔		✔	12	7	9	4
Cardiac index	✘	✘	✔						✔			✘	✘				✔			✘			✘		✔	10	4	7	4
Qp(i)		✔													✘					✘						3	1	2	2
SvO2			✔						✔																	2	2	2	2
PAC(i)																				✔			✘			2	1	1	1
PVR/SVR	✘																✔									2	1	2	2
Acute vasodilator response	✘		✔						✘			✘					✘		✔						✔	7	3	4	4
PVR during VRT										✔		✔														2	2	2	1
mPAP during VRT												✔							✔							2	2	2	2
PFR during VRT																			✔							1	1	1	1
mRAP x PVRi		✔																								1	1	1	1
PSVi																				✔						1	1	1	1
Imaging																													
Echocardiography[b]										✔	✔	✔									✘	✔	✔			6	5	6	3

Table 2. Variables associated with survival, per study (continued)

	Sandoval 1995 [14]	Clabby 1997 [26]	Barst 1999 [15]	Nakayama 2007 [24]	Van Albada 2008 [22]	Bernus 2009 [23]	Haworth 2009 [49]	Lammers 2009 [25]	Van Loon 2010 [3]	Lammers 2010 [27]	Alkon 2010 [50]	Moledina 2010 [17]	Ivy 2010 [21]	Hislop 2011 [19]	Moledina 2011 [20]	Van Loon 2011 [51]	Barst 2012 [16]	Chida 2012 [52]	Apitz 2012 [53]	Douwes 2013 [18]	Moledina 2013 [41]	Kassem 2013 [54]	Wagner 2013 [13]	Chida 2014 [55]	Zijlstra 2014 [4]	N times studied	N times significant	N extractable HRs[a]	N HRs from non-overlapping cohorts
CMR[c]																					✔					1	1	1	1
CT, fractal dimensions															✔											1	1	1	1

✔ = significant association with survival; ✘ = no significant association with survival; grey indicates that sufficient survival analysis results were provided in the paper to be included in meta-analysis; HR = hazard ratio; WHO-FC = WHO functional class; 6MWT = 6-minute walk test; RR = blood pressure; BSA = body surface area; VO2 = oxygen consumption; VE/VCO2 = ventilatory-efficiency slope; BMPR2 = bone morphogenetic protein receptor type II; (NT-pro)BNP = (N-terminal pro) brain natriuretic peptide; Hb = hemoglobin; Apo-A1 = apolipoprotein-A-1; TIMP-1 = metallopeptidase-inhibitor-1; sST2 = soluble ST2; mRAP = mean right atrial pressure; mPAP = mean pulmonary artery pressure; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; PVRi = indexed pulmonary vascular resistance; Qp(i) = pulmonary blood flow (index); SvO2 = mixed venous oxygen saturation; PAC(i) = pulmonary arterial capacitance (index); PVR/SVR = pulmonary-to-systemic vascular resistance ratio; VRT = vasoreactivity testing; PFR = pulmonary flow reserve; PSVi = pulmonary stroke volume index; CMR = cardiac magnetic resonance imaging; CT = computed tomography.

[a] HR was only extractable when sufficient survival analysis results were provided in the paper.

[b] Echocardiographic variables once shown to be associated with survival include: semi-quantitatively assessed RV-hypertrophy, RV-dilatation and RV-function (score 1-4), systolic to diastolic duration ratio, maximum tricuspid regurgitation velocity, RV-fractional area change, Z-score of tricuspid annular plane systolic excursion, Z-score of RV end-diastolic area, RV end systolic area index and right to left ventricular dimension ratio.

[c] CMR variables once shown to be associated with survival include: RV end-diastolic volume index, RV end-systolic volume index, RV ejection fraction, RV mass index, LV stroke volume index, tricuspid regurgitation fraction, right atrial area index, and mid right ventricle diameter index.

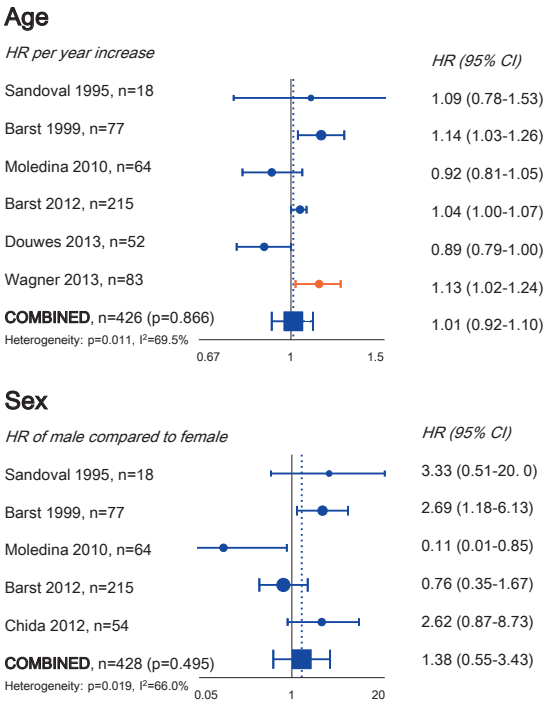

Figure 2. Forest plots showing demographic candidate prognostic factors
HRs displayed as diamonds ♦ are based on dichotomized variables, HRs displayed as dots • are based on continuous variables. Area of each diamond/dot is proportional to the sample size of the studied cohort. Only HRs in blue are non-overlapping and included in meta-analysis.
HR = hazard ratio; CI = confidence interval.

Barst 2012 and Wagner[13-16]) and European studies (Moledina and Douwes[17,18]) reported contradictory findings.

Sex was investigated in 10 studies, with HRs available from 5/10 studies (Table 2). Combining these 5 non-overlapping cohorts representing 428 patients yielded a HR (CI) of 1.38 (0.55-3.43) for male compared to female (Figure 2, p=0.495), indicating no significant association with survival.

Diagnosis was investigated in 9 studies, with HRs available from 2 studies and survival curves available from 5 studies (Table 2). Four of these 7 were omitted from meta-analysis to prevent duplicate patient inclusion (Figure 3).[3,4,18,19] Combining the remaining 3 non-overlapping cohorts representing 585 patients yielded a HR (CI) of 0.70 (0.41-1.19) for associated PAH (APAH) compared to IPAH (Figure 3, p=0.191), indicating no significant association with survival.

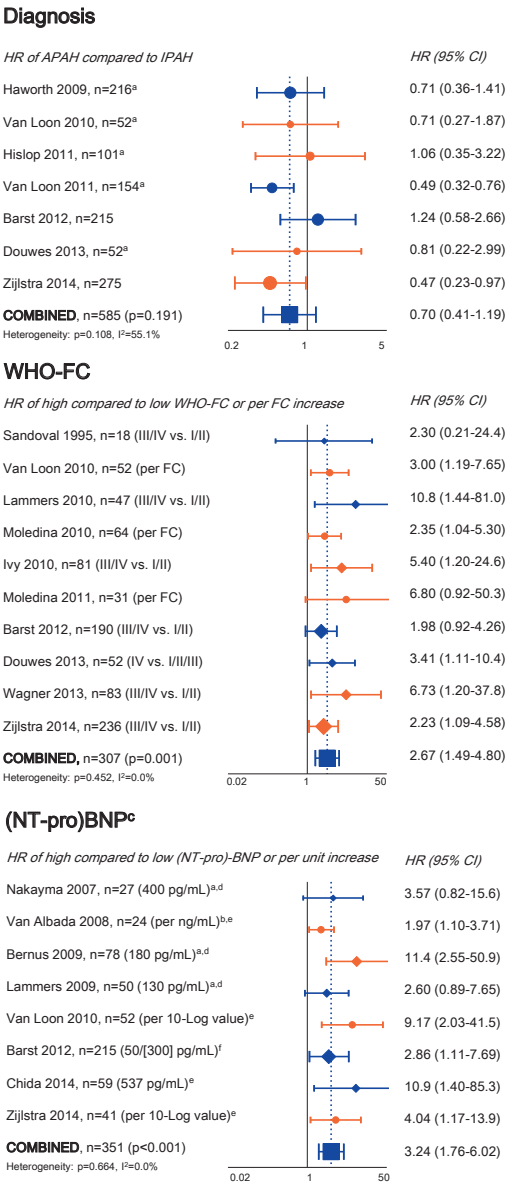

Figure 3. Forest plots showing clinical and biochemical candidate prognostic factors

HRs displayed as diamonds ♦ are based on dichotomized variables, HRs displayed as dots • are based on continuous variables. Area of each diamond/dot is proportional to the sample size of the studied cohort. Only HRs in blue are non-overlapping and included in meta-analysis. [a] HR estimated from survival curve. [b] HR calculated from reported individual patient data. [c] Between brackets are the cut-off values used in dichotomization or the number of units increase at which the HR calculation was based. [d] Studied biomarker was BNP. [e] Studied biomarker was NT-proBNP. [f] Both BNP and NT-proBNP were studied.

HR = hazard ratio; CI = confidence interval; APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; FC = functional class; (NT-pro)BNP = (N-terminal-pro) brain natriuretic peptide.

World Health Organization functional class (WHO-FC) was investigated in 11 studies, with HRs available from 10/11 studies (Table 2). Since WHO-FC was mostly studied as a dichotomized variable, 3 studies that reported HRs based on WHO-FC as a continuous variable were omitted from meta-analysis (Figure 3).[3,17,20] An additional 3 studies were omitted to prevent duplicate patient inclusion.[4,13,21] Combining the remaining 4 non-overlapping cohorts representing 307 patients yielded a HR (CI) of 2.67 (1.49-4.80), for high compared to low WHO-FC (Figure 3, p=0.001), without substantial heterogeneity-evidence (p=0.452, I^2=0.0%).

(N-Terminal-pro) brain natriuretic peptide ([NT-pro]BNP) was investigated in 9 studies (Table 2, 4x BNP, 3x NT-proBNP, 2x both) and the results of these studies were combined. HRs, survival curves and individual patient data were available from 4, 3 and 1 studies, respectively (Figure 3). Since (NT-pro)BNP was mostly studied as a dichotomized variable, 3 studies that reported HRs based on (NT-pro)BNP as a continuous variable were omitted from meta-analysis.[3,4,22] One additional study was omitted to prevent duplicate patient inclusion.[23] Combining the 4 remaining non-overlapping cohorts representing 351 patients yielded a HR (CI) of 3.24 (1.76-6.02) for high levels compared to low (Figure 3, p<0.001), without substantial heterogeneity-evidence (p=0.664, I^2=0.0%).

To be able to selectively analyze BNP instead of analyzing BNP and NT-proBNP together, we performed a sensitivity analysis. In the studies of Nakayama et al., Bernus et al., and Lammers et al., BNP was studied exclusively.[23-25] Combining these 3 non-overlapping cohorts representing 155 patients yielded a HR (CI) of 4.24 (1.80-9.96) for high levels compared to low (Supplemental file, Figure A.1, p=0.001), without substantial heterogeneity-evidence (p=0.284, I2=20.5%). A similar separate analysis for NT-proBNP was hampered by the low number of non-overlapping cohorts in which NT-proBNP was studied exclusively (n=2).

Mean right atrial pressure (mRAP) was investigated in 9 studies, with HRs available from 6/9 studies (Table 2). Since mRAP was mostly studied as a continuous variable, 1 study that reported a HR based on dichotomized mRAP was omitted from meta-analysis (Figure 4).[14] An additional 2 studies were omitted to prevent duplicate patient inclusion.[26,27] Combining the remaining 3 non-overlapping cohorts representing 404 patients yielded a HR (CI) of 1.12 (1.05-1.20) per mmHg increase (Figure 4, p=0.001), without substantial heterogeneity-evidence (p=0.289, I^2=19.3%).

Mean pulmonary artery pressure (mPAP) was investigated in 11 studies, with HRs available from 7/11 studies (Table 2). Since mPAP was mostly studied as a continuous variable, 1 study that reported a HR based dichotomized mPAP was omitted from meta-analysis (Figure 4).[14] An additional 2 studies were omitted to prevent duplicate patient inclusion.[26,27] Combining the remaining 4 non-overlapping cohorts representing 254 patients yielded a HR (CI) of 1.18 (0.99-1.40) per mmHg increase (Figure 4, p=0.056), without substantial heterogeneity-evidence (p=0.289, I^2=19.3%).

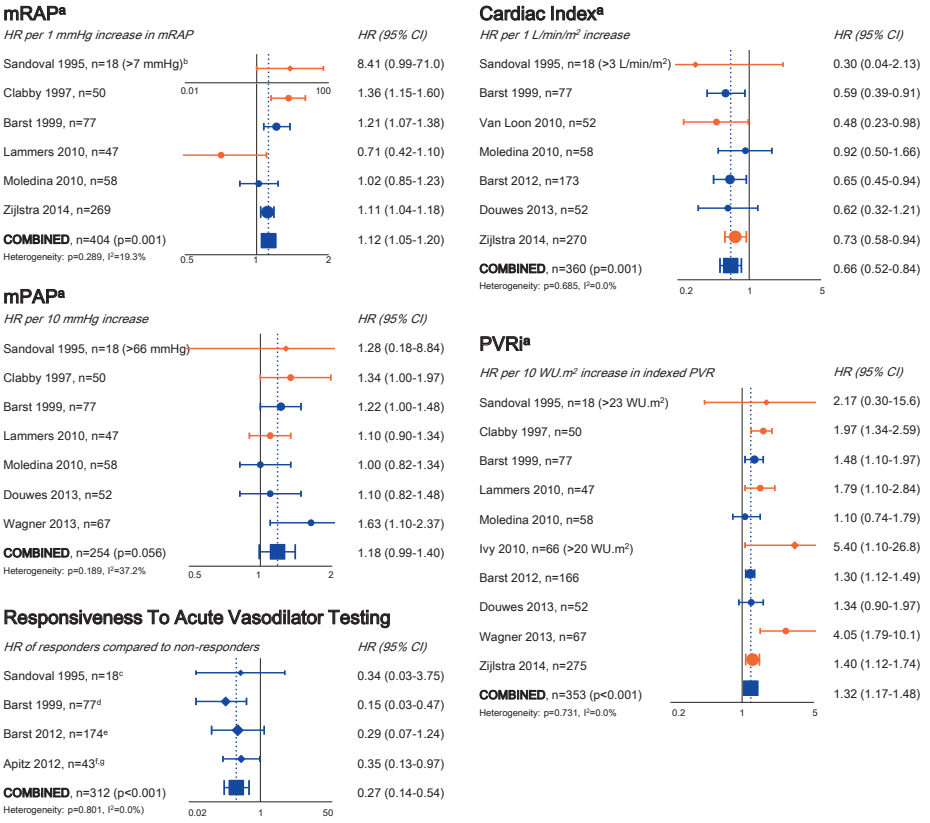

Figure 4. Forest plots showing hemodynamic candidate prognostic factors

HRs displayed as diamonds ♦ are based on dichotomized variables, HRs displayed as dots • are based on continuous variables. Area of each diamond/dot is proportional to the sample size of the studied cohort. Only HRs in blue are non-overlapping and included in meta-analysis. [a] Between brackets are the cut-off values used in dichotomization of the variable at which the HR calculation was based. [b] Because of the high HR and wide 95% CI, this study is shown on a different scale. [c] Response defined as (1) ≥20% decrease in mPAP or PVRi, (2) no decrease in pulmonary/systemic vascular resistance ratio and (3) absence of a deleterious effect on pulmonary gas exchange. [d] Response defined as (1) ≥20% decrease in mPAP, (2) no decrease in cardiac index and (3) no increase in pulmonary/systemic vascular resistance ratio. [e] Response defined as (1) ≥20% decrease in mPAP, (2) no decrease in cardiac index <2.5 L/min/m^2 and (3) no increase in pulmonary/systemic vascular resistance ratio. [f] Response defined as >20% reduction of mean pulmonary artery pressure/mean systemic artery pressure ratio. [g] HR estimated from survival curve.

mRAP = mean right atrial pressure; HR = hazard ratio; CI = confidence interval; mPAP = mean pulmonary artery pressure; PVRi = indexed pulmonary vascular resistance; WU = wood units.

Cardiac index was investigated in 10 studies, with HRs available in 7/10 studies (Table 2). Since cardiac index was mostly studied as a continuous variable, 1 study that reported a HR based dichotomized cardiac index was omitted from meta-analysis (Figure 4).[14] An additional 2 studies were omitted to prevent duplicate patient inclusion.[3,4] Combining the remaining 4 non-overlapping cohorts representing 360 patients yielded a HR

(CI) of 0.66 (0.52-0.84) per L/min/m^2 increase (Figure 4, p=0.001), without substantial heterogeneity-evidence (p=0.685, I^2=0.0%).

Indexed pulmonary vascular resistance (PVRi) was investigated in 12 studies, with HRs available in 10/12 studies (Table 2). Since PVRi was mostly studied as a continuous variable, 2 studies that reported a HR based on dichotomized PVRi were omitted from meta-analysis (Figure 4).[14,21] An additional 4 studies were omitted to prevent duplicate patient inclusion.[4,13,26,27] Combining the remaining 4 non-overlapping cohorts representing 353 patients yielded a HR (CI) of 1.32 (1.17-1.48) per 10 Wood units.m^2 increase (Figure 4, p<0.001), without substantial heterogeneity-evidence (p=0.731, I^2=0.0%).

Acute vasodilator response was investigated in 7 studies, with HRs and survival curves available from 3 and 1 studies, respectively (Table 2). It must be noted that the used vasodilators and definitions of a favorable response differed in these studies (Figure 4). Still, combining these 4 non-overlapping cohorts representing 312 patients yielded a HR (CI) of 0.27 (0.14-0.45) for responders compared to non-responders (Figure 4, p<0.001), without substantial heterogeneity-evidence (p=0.801, I^2=0.0%).

Other variables. Table 2 shows that imaging modalities have also been studied more than once (5x echocardiography, 1x cardiac magnetic resonance imaging [CMR]). None of the investigated echo-variables has been studied more than once in the same way, hampering further comparison or meta-analysis.

Table 3. Combined prognostic value of candidate prognostic factors

Predictor	N	HR (CI)	P-value
Demographic			
Age, per year	426	1.01 (0.92-1.10)	0.866
Sex, male compared to female	428	1.38 (0.55-3.43)	0.495
Clinical/biochemical			
Diagnosis, APAH compared to IPAH	585	0.70 (0.41-1.19)	0.191
WHO-FC (high compared to low)	307	2.67 (1.49-4.80)	0.001
(NT-pro)BNP	351	3.24 (1.76-6.02)	<0.001
Hemodynamic			
mRAP, per mmHg	404	1.12 (1.05-1.20)	0.001
mPAP, per 10 mmHg	254	1.18 (0.99-1.40)	0.056
Cardiac index, per 1 L/min/m^2	360	0.66 (0.52-0.84)	0.001
PVRi, per 10 WU.m^2	353	1.32 (1.17-1.48)	<0.001
Acute vasodilator response	312	0.27 (0.14-0.54)	<0.001

Data presented as hazard ratio (95% confidence interval). HR = hazard ratio; CI = 95% confidence interval; APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; WHO-FC = WHO functional class; (NT-pro)BNP = (N-terminal-pro) brain natriuretic peptide; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PVRi = (indexed) pulmonary vascular resistance; WU = wood units.

DISCUSSION

To our knowledge, this is the first study systematically reviewing and meta-analyzing all currently available prognostic factors in pediatric PAH. Separate meta-analyses for candidate prognostic factors showed convincing evidence for the prognostic value of the following six variables: WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response.

Systematic reviews combined with meta-analyses are powerful methods for summarizing and synthesizing data and are the building blocks of evidence-based practice. The highest level of evidence is reached when only randomized studies are included in a systematic review, but the available systematic reviews in adults show that this is not possible in a rare disease like PAH.[6,28] As stated by the Cochrane Collaboration, a systematic review of non-randomized observational studies is justified when the question of interest cannot be answered by a review of randomized trials.[29] As only one randomized trial has been performed in children with PAH, this justification especially applies to the field of pediatric PAH.[30,31]

Prognostic factors have also been systematically reviewed in adult PAH.[6,7,28] Well-established predictors of mortality in adults include: WHO-FC, heart rate, 6-minute walk distance (6MWD), (NT-pro)BNP, pericardial effusion, tricuspid annular plane systolic excursion, mPAP, mRAP, cardiac index, stroke volume index, PVR, acute vasodilator response and mixed venous oxygen saturation. The six prognostic factors identified in the current study are highly in line with adult evidence. However, an important difference between adult and pediatric PAH is the available evidence for 6MWD as a prognostic factor. Whereas 6MWD has repeatedly and consistently been shown to predict survival in adults[2,32], the prognostic value of 6MWD in children has been questioned because of its limited feasibility at young age and the lack of available data (Table 2). More pediatric research is needed on this topic and might focus on the prognostic value of 6MWD in older children (e.g. ≥7 years).

Several recommendations regarding the clinical assessment of prognosis have been made in current adult treatment guidelines.[5] Since the results from the current systematic review provide an overview of evidence for prognostic factors specifically in pediatric PAH, such recommendations are now also possible for children.

Prognostic factors with moderate to high level of evidence

WHO-FC. The applicability of WHO-FC in young children has been questioned in the past, because it is mainly based on the observation and impression of caregivers. Despite this apparent limitation, the current study shows WHO-FC to be one of the strongest prognostic factors in pediatric PAH, also in the relatively younger pediatric cohorts. Not all studies on WHO-FC could be included in meta-analysis because of potential

patient-overlap, but combining 4 non-overlapping cohorts showed a strong association with survival which was consistent with the results of the 6 excluded studies. The results support the recent consensus statement from the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) held in Nice, France, 2013, which proposes to strive for WHO-FC I or II as a treatment goal in pediatric PAH.[33] Treatment-induced changes in WHO-FC carry prognostic value in both adults and children, which further underscores its usefulness and validity as a pediatric treatment goal.[34-36]

(NT-pro)BNP. Pediatric studies that evaluated the prognostic value of (NT-pro)BNP differed regarding the biomarker under study (BNP, NT-proBNP or both), the used cut-off values and the analysis techniques. Nevertheless, there was a high degree of consistency and a strong association with survival in the combined meta-analysis. A sensitivity analysis with solely inclusion of studies that studied BNP, also showed a significant association with survival. It has recently been shown that children who stay on NT-proBNP levels below 1200 ng/L during treatment have significantly better survival rates, which is in line with adult findings regarding this topic.[34,36] This suggests that a low NT-proBNP level is not only a strong predictor of survival, but is also a valid treatment goal to be used in pediatric goal-oriented treatment strategies.

Hemodynamic variables. Cardiac catheterization in childhood often requires sedation or general anesthesia and has been reported to be accompanied by a complication rate of 4-6%.[37] However, the fact that 4 of the 6 identified prognostic factors in this study are hemodynamic measures underlines the importance of cardiac catheterization, at least to assess disease severity and prognosis at time of diagnosis.

Prognostic factors with low level of evidence

Although not statistically significant, APAH appeared to have a slightly more favorable prognosis compared to IPAH. Importantly, it must be noted that the meta-analysis concerning diagnosis was based upon HRs that were predominantly estimated from survival curves using Parmar's survival curve method.[10,38] This method is known to lead to underestimations of the HRs in smaller sample sizes, which subsequently could have led to an underestimation of the combined HR.[39] In addition, all subtypes of APAH were analyzed together, while differences in prognostic value might exist within this group.

Other biomarkers than (NT-pro)BNP have also been shown to correlate with survival in pediatric PAH. The current systematic literature search showed that uric acid was a significant prognostic factor in 3 separate studies based on 2 non-overlapping cohorts (Table 2). Although uric acid was not frequently enough studied to be combined in meta-analysis, this indicates at least a low level of evidence for this prognostic factor.

Although meta-analysis could not be performed for echocardiography, this imaging modality has repeatedly been shown to yield important measures for prognosis (Table 2). Echocardiography is a generally accessible follow-up tool without the need

for sedation or anesthesia and its role in assessing prognosis is already well established in adults.[40] Five pediatric studies showed echocardiographic variables to be associated with survival (Table 2), which makes this modality a promising tool in managing pediatric PAH. Further research is needed to enhance the body of evidence regarding these prognostic factors with low level of evidence.

Potential prognostic factors requiring further study

Other variables that were reported not sufficiently frequent to be meta-analyzed but may be potential prognostic factors include heart rate, blood pressure, height and weight, body surface area, heart rate variability, peak oxygen consumption, ventilatory-efficiency slope, genetic mutations, hemoglobin, norepinephrine, Apolipoprotein-A-1, metallopeptidase-inhibitor-1 and soluble ST2 (Table 2). Future research should reveal which role these variables could play in assessing prognosis in pediatric PAH.

The prognostic value of CMR has only been studied incidentally in children and the accessibility to required infrastructure and expertise may not be widely available.[41] However, the well established role of CMR in adults makes this a promising future imaging modality in addition to echocardiography also in pediatric PAH.[42]

Of special future interest in relation to survival are measures of pulmonary artery capacitance, pulmonary artery distensibility, RV stroke work, and ventricular-vascular coupling, which to date have only been studied incidentally and anecdotally in relatively small cohorts.[11,18,43-45] The feasibility and potential prognostic value of combining imaging modalities and cardiac catheterization are also under study and are expected to yield valuable insights in pulmonary arterial wall dynamics.[44]

Strengths and limitations

This recapitulation of published evidence for prognostic factors in pediatric PAH provides a unique clinical overview. Combining only randomized controlled trials would have been the most ideal way to identify prognostic factors. However, such trials reporting on prognostic factors are unavailable in this field. This could have led to a certain degree of heterogeneity, which was addressed in the current study by combining only studies with similar methodologies and providing a detailed description of the study characteristics (Table 1). Heterogeneity was tested for every meta-analyzed candidate prognostic factor, and revealed no substantial heterogeneity-evidence for the six identified statistically significant prognostic factors.

When HRs were not available, these were estimated using Parmar's survival curve method, which is known to lead to underestimations of the hazard ratios in smaller sample sizes.[39] HRs of statistically insignificant associations were sometimes not reported and could in those cases not be included in meta-analysis. Since this could potentially have led to an overrepresentation of significant results in the combined HR,

these excluded studies are shown in tabular form to avoid bias within the current paper (Table 2).

We aimed to prevent duplicate patient representation in the meta-analyses. This was accomplished by restricting study inclusion to non-overlapping cohorts. Overlap was suspected in case of overlapping inclusion periods in studies performed at the same center. Although conservative and accompanied by the risk of also excluding non-overlapping patients, this method ensured a pure and unbiased combined HR.

Considerations regarding future research

This study demonstrates the usefulness of the currently available literature on pediatric PAH. Nevertheless, available data are limited by relatively small sample sizes, insufficiently explained discrepancies and inevitable potential duplicate patient inclusion. Current international collaborative initiatives aim to overcome these limitations. The ongoing Tracking Outcomes and Practice in Pediatric PH (TOPP) registry encompasses the largest cohort of children with PAH to date and is expected to yield important new insights in survival and prognostic factors in pediatric PAH.[46] Although a powerful tool with regard to sample size, the usefulness of any registry depends on the predefined aims and might be hampered by the fact that frequency and mode of follow-up are often not dictated.[47]

To be able to further investigate reported discrepancies and to increase sample size and statistical power, it could also be considered to merge existing patient cohorts on an individual patient level. Recently, a direct comparison has been made between three major pediatric PAH referral centers, which allowed for analyzing differences in survival rates between centers.[4] Such initiatives could be further expanded in the future. To provide transparency in the degree of duplicate patient inclusion throughout different reports, it could be considered to publish lists of unique patient codes with every paper.

To be able to identify which prognostic factors could also qualify in defining treatment goals, future research should also focus on assessing the prognostic value of treatment-induced changes in these variables.[34,48]

Conclusions

This systematic review combined with separate meta-analyses shows that WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response are consistently reported prognostic factors in pediatric PAH. These variables are validated and useful clinical tools to assess prognosis. The current recapitulation of scientific evidence will provide an important basis for defining treatment strategies and developing practice guidelines for children with PAH. This systematic review does not preclude the potential of the other reported candidate prognostic factors, but rather identifies directions for further research to address gaps in current evidence.

REFERENCES

1. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease: Pulmonary arterial hypertension. Nat Rev Cardiol. 2011;8(8):443-455.
2. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation. 2010;122(2):164-172.
3. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
4. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
5. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30(20):2493-2537.
6. Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: A systematic review of the literature. Respir Med. 2010;104(11):1588-1607.
7. McCrory DC, Coeytaux RR, Schmit KM, et al. Pulmonary Arterial Hypertension: Screening, Management and Treatment, Comparative Effectiveness Review No. 117, Agency for Healthcare Research and Quality, Rockville (MD). 2013.
8. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
9. Altman DG, Bland JM. How to obtain the confidence interval from a P value. BMJ. 2011;343:d2090.
10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815-2834.
11. Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease: Relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J. 2011;162(3):562-568.
12. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660-665.
13. Wagner BD, Takatsuki S, Accurso FJ, Ivy DD. Evaluation of circulating proteins and hemodynamics towards predicting mortality in children with pulmonary arterial hypertension. PLoS One. 2013;8(11):e80235.
14. Sandoval J, Bauerle O, Gomez A, Palomar A, Martinez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: Clinical characterization and survival. J Am Coll Cardiol. 1995;25(2):466-474.
15. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
16. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
17. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.

18. Douwes JM, Roofthooft MT, Bartelds B, Talsma MD, Hillege HL, Berger RM. Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension. Int J Cardiol. 2013;168(2):1370-1377.
19. Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J. 2011;38(1):70-77.
20. Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: A proof of principle study. Heart. 2011;97(15):1245-1249.
21. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
22. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res. 2008;63(3):321-327.
23. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest. 2009;135(3):745-751.
24. Nakayama T, Shimada H, Takatsuki S, et al. Efficacy and limitations of continuous intravenous epoprostenol therapy for idiopathic pulmonary arterial hypertension in japanese children. Circ J. 2007;71(11):1785-1790.
25. Lammers AE, Hislop AA, Haworth SG. Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol. 2009;135(1):21-26.
26. Clabby ML, Canter CE, Moller JH, Bridges ND. Hemodynamic data and survival in children with pulmonary hypertension. J Am Coll Cardiol. 1997;30(2):554-560.
27. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. Int J Cardiol. 2010;142(2):159-165.
28. Lefevre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: A systematic review and meta-analysis. Arthritis Rheum. 2013;65(9):2412-2423.
29. Reeves BC, Deeks JD, Higgins JPT, Wells GA. Including non-randomized studies. In: Higgins JPT, Green S, eds. The Cochrane Collaboration. 2008.
30. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012;125(2):324-334.
31. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014.
32. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161:487-492.
33. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
34. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J. 2014;44(6):1616-1626.
35. Barst RJ, Chung L, Zamanian RT, Turner M, McGoon MD. Functional class improvement and 3-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL registry. Chest. 2013;144(1):160-168.

36. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2012;39(3):589-596.
37. Beghetti M, Berger RM, Schulze-Neick I, et al. Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. Eur Respir J. 2013;42(3):689-700.
38. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
39. Hirooka T, Hamada C, Yoshimura I. A note on estimating treatment effect for time-to-event data in a literature-based meta-analysis. Methods Inf Med. 2009;48(2):104-112.
40. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39(7):1214-1219.
41. Moledina S, Pandya B, Bartsota M, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(3):407-414.
42. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007;28(10):1250-1257.
43. Ivy DD, Neish SR, Knudson OA, et al. Intravascular ultrasonic characteristics and vasoreactivity of the pulmonary vasculature in children with pulmonary hypertension. Am J Cardiol. 1998;81(6):740-748.
44. Berger RM, Cromme-Dijkhuis AH, Hop WC, Kruit MN, Hess J. Pulmonary arterial wall distensibility assessed by intravascular ultrasound in children with congenital heart disease: An indicator for pulmonary vascular disease? Chest. 2002;122(2):549-557.
45. Di Maria MV, Younoszai AK, Mertens L, et al. RV stroke work in children with pulmonary arterial hypertension: Estimation based on invasive haemodynamic assessment and correlation with outcomes. Heart. 2014;100(17):1342-1347.
46. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
47. Berger RM. Pulmonary hypertension: Smaller kids, smaller steps. Lancet Respir Med. 2014;2(5):348-350.
48. Ventetuolo CE, Gabler NB, Fritz JS, et al. Are hemodynamics surrogate end points in pulmonary arterial hypertension? Circulation. 2014;130(9):768-775.
49. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
50. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol. 2010;106(3):430-436.
51. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
52. Chida A, Shintani M, Yagi H, et al. Outcomes of childhood pulmonary arterial hypertension in BMPR2 and ALK1 mutation carriers. Am J Cardiol. 2012;110(4):586-593.
53. Apitz C, Zimmermann R, Kreuder J, et al. Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2012;60(2):157-164.
54. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J. 2013;165(6):1024-1031.

55. Chida A, Sato H, Shintani M, et al. Soluble ST2 and N-terminal pro-brain natriuretic peptide combination. useful biomarker for predicting outcome of childhoodpulmonary arterial hypertension. Circ J. 2014;78(2):436-442.

SUPPLEMENTARY DATA

Table A.2. Studies included during full text review

First author	Abbreviated Journal Title	Year	Study Site	N	Inclusion period
Sandoval [1]	J Am Coll Cardiol	1995	Mexico City	18	1977 - 1991
Clabby [2]	J Am Coll Cardiol	1997	US multicenter	50	1982 - 1992
Barst [3]	Circulation	1999	New York	77	1982 - 1995
Yung [4]	Circulation	2004	New York	44	1982 - 1995
Nakayama [5]	Circ J	2007	Tokyo	31	1999 - 2004
Van Albada [6]	Pediatr Res	2008	Netherlands	29	1997 - 2005
Bernus [7]	Chest	2009	Denver	78	2005 - 2008
Haworth [8]	Heart	2009	London	216	2001 - 2006
Lammers [9]	Int J Cardiol	2009	London	50	2004 - 2006
Van Loon [10]	Am J Cardiol	2010	Netherlands	52	1993 - 2008
Lammers [11]	Int J Cardiol	2010	London	47	Not reported
Alkon [12]	Am J Cardiol	2010	Toronto	47	1999 - 2008
Moledina [13]	Heart	2010	London	64	2001 - 2007
Ivy [14]	Am J Cardiol	2010	New York and Denver	86	2001 - 2003
Hislop [15]	Eur Respir J	2011	London	101	2002 - 2008
Moledina [16]	Heart	2011	London	31	2007 - 2009
Sajan [17]	Am Heart J	2011	Toronto	47	1996 - 2007
Van Loon [18]	Circulation	2011	Netherlands	154	1991 - 2006
Barst [19]	Circulation	2012	US multicenter	216	2006 - 2009
Chida [20]	Am J Cardiol	2012	Japan/China multicenter	54	1995 - 2011
Apitz [21]	J Am Coll Cardiol	2012	Giessen	43	Not reported
Douwes [22]	Int J Cardiol	2013	Groningen	52	1993 - 2010
Moledina [23]	Circ Cardiovasc Imaging	2013	London	100	2007 - 2012
Kassem [24]	Am Heart J	2013	Toronto	54	2004 - 2011
Wagner [25]	Plos One	2013	Denver	83	2001 - 2008
Chida [26]	Circ J	2014	Tokyo	59	Not reported
Zijlstra [27]	J Am Coll Cardiol	2014	NL + Denver + New York	275	2000 - 2010

Citations are listed in a supplementary references section within this data supplement.
US = United States; NL = Netherlands.

Table A.1. Search strings used and number of identified abstracts per literature database

	MEDLINE	n hits	EMBASE	n hits	Cochrane Library	n hits
Component #1 'PAH'	"Pulmonary arterial hypertension"[title/abstract] OR "primary pulmonary hypertension"[title/abstract] OR "IPAH"[title/abstract] OR "pediatric pulmonary hypertension"[title/abstract]	8419	('Pulmonary arterial hypertension':ti,ab OR 'primary pulmonary hypertension':ti,ab OR 'IPAH':ti,ab OR 'pediatric pulmonary hypertension':ti,ab) AND [embase]/lim	10738	"Pulmonary arterial hypertension":ti,ab OR "primary pulmonary hypertension":ti,ab OR "IPAH":ti,ab OR "pediatric pulmonary hypertension":ti,ab	419
Component #2 'Children'	"Pediatrics"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR Pediatric[title/abstract] OR Pediatrics [title/abstract] OR Paediatric[title/abstract] OR Paediatrics[title/abstract] OR child[title/abstract] OR children[title/abstract] OR childhood[title/abstract] OR kids[title/abstract] OR adolescent[title/abstract] OR adolescents[title/abstract] OR adolescence[title/abstract] OR infant[title/abstract] OR infants[title/abstract] OR infancy[title/abstract] OR baby[title/abstract] OR babies[title/abstract]	3119773	(('Pediatrics'/exp OR 'Child'/exp OR 'Adolescent'/exp OR 'Infant'/exp) OR (Pediatric:ti,ab OR Pediatrics:ti,ab OR Paediatric:ti,ab OR Paediatrics:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR kids:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR adolescence:ti,ab OR infant:ti,ab OR infants:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab)) AND [embase]/lim	1928580	((MeSH descriptor Pediatrics explode all trees) OR (MeSH descriptor Child explode all trees) OR (MeSH descriptor Adolescent explode all trees) OR (MeSH descriptor Infant explode all trees)) OR (Pediatric:ti,ab OR Pediatrics:ti,ab OR Paediatric:ti,ab OR Paediatrics:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR kids:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR adolescence:ti,ab OR infant:ti,ab OR infants:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab)	77154
Component #3 'Survival'	"Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "Mortality"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Treatment Outcome"[Mesh] OR "Prognosis"[Mesh] OR Survival[title/abstract] OR mortality[title/abstract] OR Prognosis[title/abstract] OR death[title/abstract] OR deaths[title/abstract] OR outcome[title/abstract] OR outcomes[title/abstract]	2792649	(('Survival'/exp OR 'Proportional Hazards Model'/exp OR 'Survival Rate'/exp OR 'Mortality'/exp OR 'Outcome Assessment'/exp OR 'Treatment Outcome'/exp OR 'Prognosis'/exp) OR (Survival:ti,ab OR mortality:ti,ab OR Prognosis:ti,ab OR death:ti,ab OR deaths:ti,ab OR outcome:ti,ab OR outcomes:ti,ab)) AND [embase]/lim	2918321	((MeSH descriptor Survival explode all trees) OR (MeSH descriptor Survival Analysis explode all trees) OR (MeSH descriptor Survival Rate explode all trees) OR (MeSH descriptor Mortality explode all trees) OR (MeSH descriptor Outcome Assessment (Health Care) explode all trees) OR (MeSH descriptor Treatment Outcome explode all trees) OR (MeSH descriptor Prognosis explode all trees)) OR (Survival:ti,ab OR mortality:ti,ab OR Prognosis:ti,ab OR death:ti,ab OR deaths:ti,ab OR outcome:ti,ab OR outcomes:ti,ab)	150197
Combined search #4	#1 AND #2 AND #3	746	#1 AND #2 AND #3	705	#1 AND #2 AND #3	9

Values represent the number of identified abstracts for every separate search string at April 1st 2014. Combining the final MEDLINE, EMBASE and Cochrane searches yielded 1053 unique abstracts. PAH = pulmonary arterial hypertension.

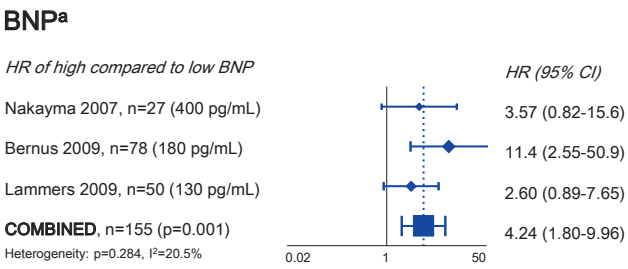

Figure A.1. Forest plot showing combined prognostic value of brain natriuretic peptide
Area of each diamond u is proportional to the sample size of the studied cohort. [a] HRs are estimated from survival curve. Between brackets are the cut-off values used in dichotomizing BNP.
BNP = brain natriuretic peptide; HR = hazard ratio; CI = confidence interval.

Table A.3. Studies excluded during full text review

First author	Abbreviated Journal Title	Year	Reason for exclusion
Houde [28]	Br Heart J	1993	PAH not main topic
Kerstein [29]	Circulation	1995	No survival analysis performed[a]
Darlow [30]	N Z Med J	1998	PAH not main topic
Rosenzweig [31]	Circulation	1999	No survival analysis performed[a]
Manzar [32]	J Coll Physicians Surg Pak	2004	PAH not main topic
Humpl [33]	Circulation	2005	No survival analysis performed[a]
Rosenzweig [34]	J Am Coll Cardiol	2005	Endpoint other than Dt or Dt/LTx
Simpson [35]	J Heart Lung Transplant	2006	No survival analysis performed[a]
Lammers [36]	Heart	2007	No survival analysis performed[a]
Duffels [37]	Int J Cardiol	2007	Analysis not restricted to children
Taylor [38]	Br J Anaesth	2007	No survival analysis performed[a]
Van Loon [39]	Am Heart J	2007	Analysis not restricted to children
Fasnacht [40]	Swiss Med Wkly	2007	No survival analysis performed[a]
Joshi [41]	Perinatology	2007	PAH not main topic
Ivy [42]	J Am Coll Cardiol	2008	No survival analysis performed[a]
Kim [43]	Korean Circ J	2008	No survival analysis performed[a]
Dickinson [44]	J Heart Lung Transplant	2009	Analysis not restricted to children
Fraisse [45]	Arch Cardiovasc Dis	2010	No survival analysis performed[a]
Barst [46]	Pediatr Cardiol	2010	No survival analysis performed[a]
Melnick [47]	Am J Cardiol	2010	No survival analysis performed[a]
Goldstein [48]	J Heart Lung Transplant	2011	PAH not main topic
Schaellibaum [49]	Pediatr Pulmonol	2011	PAH not main topic
Douwes [50]	Eur Heart J	2011	Analysis not restricted to children
Takatsuki [51]	Pediatr Cardiol	2012	No survival analysis performed[a]
Yeager [52]	Proteomics Clin Appl	2012	No survival analysis performed[a]
Baruteau [53]	Ann Thorac Surg	2012	No survival analysis performed[a]
Takatsuki [54]	J Pediatr	2012	Endpoint other than Dt or Dt/LTx
Krishnan [55]	Am J Cardiol	2012	No described survival
Duncan [56]	Mediators Inflamm	2012	No survival analysis performed[a]
Siehr [57]	J Heart Lung Transplant	2013	No survival analysis performed[a]
Kömhoff [58]	Pediatrics	2013	No survival analysis performed[a]
Roofthooft [59]	Am J Cardiol	2013	Endpoint other than Dt or Dt/LTx
Rausch [60]	Int J Cardiol	2013	No survival analysis performed[a]
Maxey [61]	Pediatr Cardiol	2013	No survival analysis performed[a]
Aiello [62]	Pediatr Pulmonol	2014	No survival analysis performed[a]
Douwes [63]	Heart	2014	No survival analysis performed[a]
Waruingi [64]	World J Pediatr	2014	No survival analysis performed[a]
Barst [65]	Circulation	2014	No survival analysis performed[a]

Citations are listed in a supplementary references section within this data supplement.
[a] Survival analysis in which a candidate prognostic factor is evaluated using Cox regression analysis or Kaplan Meier analysis (not: comparison of treatment group survival).
Dt = death; Dt/Ltx = death or lung-transplantation.

SUPPLEMENTARY REFERENCES

1. Sandoval J, Bauerle O, Gomez A, Palomar A, Martinez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: Clinical characterization and survival. J Am Coll Cardiol. 1995;25(2):466-474.
2. Clabby ML, Canter CE, Moller JH, Bridges ND. Hemodynamic data and survival in children with pulmonary hypertension. J Am Coll Cardiol. 1997;30(2):554-560.
3. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
4. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660-665.
5. Nakayama T, Shimada H, Takatsuki S, et al. Efficacy and limitations of continuous intravenous epoprostenol therapy for idiopathic pulmonary arterial hypertension in japanese children. Circ J. 2007;71(11):1785-1790.
6. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res. 2008;63(3):321-327.
7. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest. 2009;135(3):745-751.
8. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
9. Lammers AE, Hislop AA, Haworth SG. Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol. 2009;135(1):21-26.
10. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
11. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. Int J Cardiol. 2010;142(2):159-165.
12. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol. 2010;106(3):430-436.
13. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
14. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
15. Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J. 2011;38(1):70-77.
16. Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: A proof of principle study. Heart. 2011;97(15):1245-1249.
17. Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease: Relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J. 2011;162(3):562-568.
18. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.

19. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
20. Chida A, Shintani M, Yagi H, et al. Outcomes of childhood pulmonary arterial hypertension in BMPR2 and ALK1 mutation carriers. Am J Cardiol. 2012;110(4):586-593.
21. Apitz C, Zimmermann R, Kreuder J, et al. Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2012;60(2):157-164.
22. Douwes JM, Roofthooft MT, Bartelds B, Talsma MD, Hillege HL, Berger RM. Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension. Int J Cardiol. 2013;168(2):1370-1377.
23. Moledina S, Pandya B, Bartsota M, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(3):407-414.
24. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J. 2013;165(6):1024-1031.
25. Wagner BD, Takatsuki S, Accurso FJ, Ivy DD. Evaluation of circulating proteins and hemodynamics towards predicting mortality in children with pulmonary arterial hypertension. PLoS One. 2013;8(11):e80235.
26. Chida A, Sato H, Shintani M, et al. Soluble ST2 and N-terminal pro-brain natriuretic peptide combination. useful biomarker for predicting outcome of childhoodpulmonary arterial hypertension. Circ J. 2014;78(2):436-442.
27. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
28. Houde C, Bohn DJ, Freedom RM, Rabinovitch M. Profile of paediatric patients with pulmonary hypertension judged by responsiveness to vasodilators. Br Heart J. 1993;70(5):461-468.
29. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation. 1995;91(7):2028-2035.
30. Darlow B, Kempthorne P, Knight D, Wong M. Audit of early experience with inhaled nitric oxide in new zealand neonatal intensive care units. N Z Med J. 1998;111(1079):474-477.
31. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99(14):1858-1865.
32. Manzar S, Nair AK, Pai MG, Al Khusaiby SM. Pulmonary hypertension in neonates: Does the cause influence the outcome? J Coll Physicians Surg Pak. 2004;14(10):612-614.
33. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: Twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation. 2005;111(24):3274-3280.
34. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(4):697-704.
35. Simpson CM, Penny DJ, Cochrane AD, et al. Preliminary experience with bosentan as initial therapy in childhood idiopathic pulmonary arterial hypertension. J Heart Lung Transplant. 2006;25(4):469-473.
36. Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. Heart. 2007;93(6):739-743.

37. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: An epidemiologic perspective from a dutch registry. Int J Cardiol. 2007;120(2):198-204.
38. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MR. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. Br J Anaesth. 2007;98(5):657-661.
39. van Loon RL, Hoendermis ES, Duffels MG, et al. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: Does the beneficial effect persist? Am Heart J. 2007;154(4):776-782.
40. Fasnacht MS, Tolsa JF, Beghetti M, Swiss Society for Pulmonary Arterial Hypertension. The swiss registry for pulmonary arterial hypertension: The paediatric experience. Swiss Med Wkly. 2007;137(35-36):510-513.
41. Joshi R, Patil SS, Dominic S, Pratap U, Rajhans AP, Devaskar UP. Is inhaled nitric oxide therapy in neonates with primary pulmonary hypertension in developing countries like india feasible? Perinatology. 2007;9:101-105.
42. Ivy DD, Doran AK, Smith KJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;51(2):161-169.
43. Kim HW, Kim GB, Je HG, et al. Pulmonary arterial hypertension in children: A single center experience. Korean Circulation Journal. 2008;38:644-650.
44. Dickinson MG, Scholvinck EH, Boonstra A, Vonk-Noordegraaf A, Snijder RJ, Berger RM. Low complication rates with totally implantable access port use in epoprostenol treatment of pulmonary hypertension. J Heart Lung Transplant. 2009;28(3):273-279.
45. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.
46. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel DL, NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol. 2010;31(5):598-606.
47. Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. Am J Cardiol. 2010;105(10):1485-1489.
48. Goldstein BS, Sweet SC, Mao J, Huddleston CB, Grady RM. Lung transplantation in children with idiopathic pulmonary arterial hypertension: An 18-year experience. J Heart Lung Transplant. 2011;30(10):1148-1152.
49. Schaellibaum G, Lammers AE, Faro A, et al. Bilateral lung transplantation for pediatric idiopathic pulmonary arterial hypertension: A multi-center experience. Pediatr Pulmonol. 2011;46(11):1121-1127.
50. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: Occurrence and prognostic value when comparing three response criteria. Eur Heart J. 2011;32(24):3137-3146.
51. Takatsuki S, Darst JR, Das BB, Fagan TE, Wolfe R, Ivy DD. Clinical manifestations and long-term follow-up in pediatric patients living at altitude with isolated pulmonary artery of ductal origin. Pediatr Cardiol. 2012;33(5):775-781.
52. Yeager ME, Colvin KL, Everett AD, Stenmark KR, Ivy DD. Plasma proteomics of differential outcome to long-term therapy in children with idiopathic pulmonary arterial hypertension. Proteomics Clin Appl. 2012;6(5-6):257-267.
53. Baruteau AE, Serraf A, Levy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: Long-term results. Ann Thorac Surg. 2012;94(3):817-824.

54. Takatsuki S, Nakayama T, Jone PN, et al. Tissue doppler imaging predicts adverse outcome in children with idiopathic pulmonary arterial hypertension. J Pediatr. 2012;161(6):1126-1131.
55. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. Am J Cardiol. 2012;110(11):1704-1709.
56. Duncan M, Wagner BD, Murray K, et al. Circulating cytokines and growth factors in pediatric pulmonary hypertension. Mediators Inflamm. 2012;2012:143428.
57. Siehr SL, Ivy DD, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: Long-term hemodynamics. J Heart Lung Transplant. 2013;32(5):546-552.
58. Komhoff M, Roofthooft MT, Westra D, et al. Combined pulmonary hypertension and renal thrombotic microangiopathy in cobalamin C deficiency. Pediatrics. 2013;132(2):e540-4.
59. Roofthooft MT, Douwes JM, Vrijlandt EJ, Berger RM. Frequency and prognostic significance of hemoptysis in pediatric pulmonary arterial hypertension. Am J Cardiol. 2013;112(9):1505-1509.
60. Rausch CM, Taylor AL, Ross H, Sillau S, Ivy DD. Ventilatory efficiency slope correlates with functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension. Int J Cardiol. 2013;169(6):445-448.
61. Maxey DM, Ivy DD, Ogawa MT, Feinstein JA. Food and drug administration (FDA) postmarket reported side effects and adverse events associated with pulmonary hypertension therapy in pediatric patients. Pediatr Cardiol. 2013;34(7):1628-1636.
62. Aiello VD, Thomaz AM, Pozzan G, Lopes AA. Capillary hemangiomatosis like-lesions in lung biopsies from children with congenital heart defects. Pediatr Pulmonol. 2014;49(3):E82-5.
63. Douwes JM, Roofthooft MT, Van Loon RL, et al. Sildenafil add-on therapy in paediatric pulmonary arterial hypertension, experiences of a national referral centre. Heart. 2014;100(3):224-230.
64. Waruingi W, Mhanna MJ. Pulmonary hypertension in extremely low birth weight infants: Characteristics and outcomes. World J Pediatr. 2014;10(1):46-52.
65. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014.

7

Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies

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ABSTRACT

Background– In pediatric PAH, discrepancies exist in reported survival rates between North American and European patient cohorts, and robust data for long-term treatment effects are lacking. In order to describe survival and treatment strategies in pediatric pulmonary arterial hypertension (PAH) in the current era of PAH-targeted drugs and to identify predictors of outcome, we studied uniformly defined contemporary patient cohorts at three major referral centers for pediatric PAH (New York [NY], Denver and the Netherlands [NL]).

Methods– According to uniform inclusion criteria, 275 recently diagnosed consecutive pediatric PAH patients who visited the 3 referral centers between 2000 and 2010 were included.

Results– Unadjusted survival rates differed between the center cohorts (1-, 3- and 5-year transplantation-free survival rates: 100%, 96%, and 90% for NY; 95%, 87%, and 78% for Denver; and 84%, 71%, and 62% for NL, respectively; $p<0.001$). Based on WHO functional class and hemodynamic parameters, disease severity at diagnosis differed between the center cohorts. Adjustment for diagnosis, WHO functional class, indexed pulmonary vascular resistance and pulmonary-to-systemic arterial pressure ratio resolved the observed survival differences. Treatment with PAH-targeted dual and triple therapy during the study period was associated with better survival than treatment with PAH-targeted mono therapy.

Conclusions– Survival rates of pediatric PAH patients differed between 3 major referral centers. This could be explained by differences between the center cohorts in patients' diagnoses and measures of disease severity, which were identified as important predictors of outcome. In this study, treatment with PAH-targeted combination therapy during the study period was independently associated with improved survival.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive pulmonary vascular disease that has a poor prognosis with a median survival of <3 years if untreated.[1] It can present at any age, including childhood, during which survival is believed to be even worse.[2,3] Substantial progress has been made in treatment strategies for adult PAH, resulting in improved quality of life and survival.[4,5] Adult studies alone do not provide a basis for optimal care for children. However, due to the virtual absence of pediatric efficacy and outcome data, these adult treatment strategies have been extrapolated to children with PAH.

Recently, survival data of pediatric PAH in the current treatment era of PAH-targeted drugs have been reported from different patient cohorts. These include 2 reports on national cohorts of children with PAH from Europe (United Kingdom and the Netherlands) and 2 reports from the United States (US), including 1 study of a cohort of children followed in 2 major US referral centers and 1 of a subgroup of patients with childhood-onset PAH included in a US-based multicenter PAH-registry (REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management]).[6-10] In all cohorts, the reported survival seemed to be improved compared to historical reports. However, intriguingly, the reported survival rates appeared to differ significantly between the European and US reports.

No direct comparisons can be made between these reported survival rates due to differences in inclusion criteria, patient characteristics, and data collection. Nevertheless, these discrepancies in survival are of interest, because they might be a consequence of varying patient characteristics or different treatment strategies adopted by the reporting centers. Therefore, they may reveal information on the importance of clinical predictors of survival and on the optimal treatment strategy.

We directly compared patient characteristics, treatment strategies, and outcomes, and identified predictors of outcome in pediatric PAH patients seen on both sides of the Atlantic Ocean, specifically those seen in 2 major referral centers in the United States (New York, New York and Denver, Colorado) and those seen in a national referral center for pediatric PAH based in Europe (the Netherlands) using similar standardized inclusion criteria.

METHODS

Patient data were retrospectively collected from 3 major referral centers for pediatric PAH: 2 US-based centers, the Children's Hospital Colorado, Denver, Colorado (Denver cohort) and Columbia University Medical Center, New York, New York (NY cohort) and 1 Europe-based center, the University Medical Center Groningen/Beatrix Children's Hospital, Groningen (Dutch cohort). The Europe-based center serves as the national

referral center for pulmonary hypertension (PH) in childhood in the Netherlands. All Dutch children with (suspected) PAH are referred to this center for diagnostic work-up, treatment, and follow-up. It therefore follows a national cohort of children with PAH.

Patients

To define patient cohorts in a way that allowed for direct comparison, we used uniform inclusion criteria: all pediatric PAH (group 1 PH, Dana Point classification[11]) patients who visited the 3 referral centers between 2000 through 2010, diagnosed by cardiac catheterization at <18 years of age, were included. Diagnosis of PAH was defined as mean pulmonary arterial pressure ≥25 mmHg, mean pulmonary capillary wedge pressure ≤15 mmHg, and pulmonary vascular resistance index (PVRi) ≥3 Wood units.m^2. To ensure similar PAH-targeted drug availability for all studied patients, only patients who visited the referral centers between 2000 and 2010 were included. To study a contemporary cohort, only patients diagnosed after 1997 were included. In patients with a corrected heart defect, diagnosis of PAH was confirmed at least 1 year after corrective surgery.[12] Patients who had pulmonary arterial pressures normalized while therapy was discontinued were considered not to have PAH because of the progressive character of the disease, and were not included. To avoid double inclusion, 1 patient who switched from one to the other US center was included in the cohort of the latter center. All patient data were uniformly collected in a database specifically designed for this study.

Patients with PH secondary to left heart disease, lung disease, thromboembolic disease, or PH with unclear multifactorial mechanisms (group 2 to 5 PH, Dana Point classification[11]) were not included in this study.

Study assessments

Patients were diagnosed according to the Clinical Classification of Pulmonary Hypertension (Dana Point update).[11] For this study, diagnosis was classified as idiopathic or hereditary PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD), or associated PAH-non-CHD (APAH-non-CHD).[12] In case of CHD, type of shunt was defined as pre-tricuspid (e.g. atrial septal defect), post-tricuspid (e.g. ventricular septal defect), repaired pre- or repaired post-tricuspid shunt, or as no previous shunt (e.g. coarctation of the aorta). Furthermore, Eisenmenger syndrome was defined as the presence of a post-tricuspid shunt with right-to-left shunting and systemic arterial, or if not available, transcutaneous, oxygen saturation of less than 90%.

Baseline parameters included clinical and hemodynamic characteristics at diagnosis. Age-normalized scores (z-scores) for height and body mass index were calculated using the World Health Organization (WHO) child growth standards.[13,14] Mean pulmonary-to-systemic arterial pressure ratios (mPAP/mSAP), pulmonary-to-systemic vascular resistance ratios and pulmonary-to-systemic blood flow ratios were calculated. Acute

responder status was determined according to criteria defined by the REVEAL study for childhood-onset PAH, Barst et al. and Sitbon et al.[10,15,16]

Specific PAH therapy was classified as either calcium channel blocker (CCB) therapy without the need of additional PAH-targeted therapy (CCB monotherapy) or as PAH-targeted therapy, including prostanoids, endothelin receptor antagonists, and type 5-phosphodiesterase inhibitors. PAH-targeted therapy was further classified as monotherapy or as combination therapy with a combination of 2 (dual therapy) or 3 PAH-targeted drugs (triple therapy) administered for at least 3 months or until end of follow-up. Real-time therapy was cumulatively plotted per center cohort for visual comparison. Furthermore, treatment strategy was defined as either CCB monotherapy when a CCB was the only specific PAH drug used during the patient's disease course, or the maximum number of simultaneously used PAH-targeted drugs (mono-, dual, or triple therapy). Also, it was determined whether therapy included an intravenously (IV) or subcutaneously (SC) administered prostanoid. Two Dutch patients and 1 Denver patient were excluded from this latter comparison because their death within 7 days after diagnosis did not allow for start of specific PAH therapy.

Statistical analysis

Data are presented as mean ± SD, median (interquartile range), and number (percentage) of patients, as appropriate. Patient characteristics, baseline parameters and treatment strategy were compared between the 3 center cohorts using one-way analysis of variance for continuous normally distributed variables, and Kruskal-Wallis test and Mann Whitney U test for ordinal and not normally distributed continuous variables. Multiple Chi square tests and Fishers exact tests were used for categorical variables. Post-hoc Bonferroni was used to correct for multiple comparisons, as appropriate.

Survival analyses were based on transplantation-free survival. Patients who did not die or undergo (heart-)lung transplantation were censored at the last recorded visit. For this study, patients who had had their last recorded visit more than 2 years before the end of the study period were considered lost to follow-up.

Survival rates were compared between the 3 center cohorts by using Kaplan-Meier curves with log rank testing. Kaplan-Meier curves were also used to illustrate the survival of the patient groups who underwent different treatment strategies. To determine predictors of survival in the total cohort, univariate Cox regression analysis was used. Multivariate backward stepwise Cox regression analysis was used to identify the strongest independent predictors of survival. P-values <0.05 were considered significant.

To assess potential overfitting, we conducted secondary sensitivity analyses using bootstrap model selection to assess independent predictors of survival. This method has been used previously in the context of a population of coronary stent thromboses to avoid an overfit model.[17] Among the variables, bootstrap selection with 500 models was performed

in the full dataset only without natriuretic peptides due to the substantial number of missing cases, the full dataset without natriuretic peptides, and blood pressure and, finally the full dataset without natriuretic peptides, blood pressure, and center (see Table 3).

RESULTS

In total, 275 pediatric patients were included in this study: 135 patients from NY, 93 patients from Denver and 47 patients from the Netherlands. Patient characteristics and clinical and hemodynamic parameters at time of diagnosis are shown in Table 1.

Table 1. Patient characteristics and clinical and hemodynamic parameters at diagnosis stratified by center cohort

	All patients		New York cohort		Denver cohort		Dutch cohort		
	N	Value	N	Value	N	Value	N	Value	P-value
Age at diagnosis, yrs	275	6.4 (2.5; 11.8)	135	7.2 (2.6; 12.1)	93	5.0 (2.5; 9.7)	47	7.9 (2.5; 13.7)	0.283
Age at first symptoms, yrs	225	5.0 (1.1; 10.1)	124	4.5 (0.6; 9.7)	55	5.1 (2.5; 10.1)	46	6.1 (0.7; 11.4)	0.260
Time from first symptoms to diagnosis, months	225	7.6 (2.2; 22.9)	124	11.7 (4.2; 29.7)	55	3.4 (0.7; 12.2)	46	4.1 (2.0; 15.1)	<0.001*†
Incident patients	275	244 (89)	135	114 (84)	93	87 (94)	47	43 (92)	0.087
Female	275	162 (59)	135	81 (60)	93	55 (59)	47	26 (55)	0.869
Ethnicity	275		135		93		47		0.004†
Caucasian		187 (68)		78 (58)		68 (73)		41 (87)	
Black		13 (5)		8 (6)		3 (3)		2 (4)	
Asian		23 (8)		17 (13)		4 (4)		2 (4)	
Hispanic		33 (12)		17 (13)		14 (15)		2 (4)	
Other or unknown		19 (7)		15 (11)		4 (4)		0	
Down syndrome	275	35 (13)	135	12 (9)	93	18 (19)	47	5 (11)	0.059
Diagnosis	275		135		93		47		0.023
IPAH/HPAH		144 (52)		76 (56)		40 (43)		28 (60)	
PAH-CHD		114 (42)		54 (40)		47 (51)		13 (28)	
No shunt		6 (5)		1 (2)		5 (11)		0	0.011‡
Pre-tricuspid shunt		13 (11)		4 (7)		8 (17)		1 (8)	
Post-tricuspid shunt		54 (47)		30 (56)		13 (28)		11 (85)	
Repaired pre-tricuspid shunt		6 (5)		2 (4)		4 (9)		0	
Repaired post-tricuspid shunt		35 (31)		17 (32)		17 (36)		1 (8)	
Eisenmenger syndrome§		14 (12)		7 (13)		3 (6)		4 (31)	0.067
APAH-non-CHD		17 (6)		5 (4)		6 (7)		6 (13)	
Symptoms at diagnosis	215		109		59		47		
Dyspnea in rest		27 (13)		13 (12)		0		14 (30)	<0.001*†‡
Dyspnea on exertion		124 (58)		63 (58)		25 (42)		36 (77)	0.002‡
Chest discomfort		29 (13)		22 (20)		5 (9)		2 (4)	0.012†
Fatigue		52 (24)		26 (24)		19 (32)		7 (15)	0.117
Syncope		36 (17)		23 (21)		4 (7)		9 (19)	0.053

Table 1. Patient characteristics and clinical and hemodynamic parameters at diagnosis stratified by center cohort (continued)

	All patients		New York cohort		Denver cohort		Dutch cohort		
	N	Value	N	Value	N	Value	N	Value	P-value
WHO functional class	236		123		67		46		0.011†‡
I		14 (6)		13 (11)		0		1 (2)	
II		107 (45)		56 (46)		40 (60)		11 (24)	
III		78 (33)		33 (27)		18 (27)		27 (59)	
IV		37 (16)		21 (17)		9 (13)		7 (15)	
Height, cm	193	119.3 ± 34.1	88	123.4 ± 32.4	63	112.3 ± 34.1	42	121.4 ± 36.7	0.131
Weight, kg	198	29.0 ± 21.1	90	31.3 ± 22.3	63	25.5 ± 19.0	45	29.2 ± 21.1	0.242
BMI, kg/m^2	192	17.8 ± 5.0	87	18.5 ± 5.6	63	17.2 ± 4.3	42	17.3 ± 4.4	0.262
Z-score height	193	-0.87 ± 1.5	88	-0.78 ± 1.27	63	-1.11 ± 1.68	42	-0.72 ± 1.61	0.295
Z-score BMI	190	-0.12 ± 1.6	87	0.07 ± 1.63	62	-0.22 ± 1.45	41	-0.36 ± 1.58	0.299
TcSO2, %	166	94 ± 7	70	95 ± 4	59	92 ± 8	37	92 ± 8	0.020
6MWD, m	72	428 ± 100	34	471 ± 71	20	444 ± 103	18	329 ± 75	<0.001†‡
Log value of NT-proBNP	41	2.85 ± 0.77		-	15	2.85 ± 0.82	26	2.85 ± 0.76	0.991
Log value of BNP	51	1.91 ± 0.63	20	2.03 ± 0.46	26	1.96 ± 0.67	5	1.33 ± 0.86	0.079
Systolic blood pressure, mmHg	190	96 ± 16	91	99 ± 12	66	87 ± 17	33	104 ± 16	<0.001*‡
Diastolic blood pressure, mmHg	181	58 ± 12	82	63 ± 10	66	51 ± 12	33	62 ± 12	<0.001*‡
mPAP, mmHg	275	55 ± 18	135	57 ± 19	93	52 ± 19	47	53 ± 16	0.094
mSAP, mmHg	273	66 ± 14	134	68 ± 14	92	66 ± 14	47	59 ± 13	<0.001†‡
mRAP, mmHg	269	6 ± 3	131	6 ± 3	92	7 ± 3	46	7 ± 4	0.241
mPCWP, mmHg	275	9 ± 3	135	8 ± 3	93	9 ± 3	47	9 ± 3	0.666
Qsi, l/min/m^2	270	3.60 ± 1.73	131	3.73 ± 1.91	93	3.67 ± 1.34	46	3.10 ± 1.85	0.089
Qpi, l/min/m^2	275	3.65 ± 1.74	135	3.86 ± 1.98	93	3.77 ± 1.53	47	2.78 ± 1.03	0.001†‡
PVRi, WU.m^2	275	15.81 ± 10.79	135	15.93 ± 10.62	93	14.01 ± 10.20	47	19.04 ± 11.83	0.032‡
SVRi, WU.m^2	252	19.78 ± 10.69	117	20.96 ± 11.80	90	18.27 ± 10.01	45	19.75 ± 8.62	0.200
mPAP/mSAP	273	0.86 ± 0.30	134	0.87 ± 0.30	92	0.81 ± 0.29	47	0.92 ± 0.30	0.095
PVR/SVR	252	0.87 ± 0.78	117	0.82 ± 0.54	90	0.79 ± 0.46	45	1.16 ± 1.47	0.021†‡
Qp/Qs	270	1.05 ± 0.31	131	1.08 ± 0.35	93	1.04 ± 0.24	46	1.00 ± 0.34	0.336
Acute vasodilator response									
Sitbon criteria	217	29 (13)	98	14 (14)	79	12 (15)	40	3 (8)	0.475
Barst criteria	203	37 (18)	88	12 (14)	75	18 (24)	40	7 (18)	0.230
REVEAL childhood criteria	203	50 (25)	88	17 (19)	75	23 (31)	40	10 (25)	0.245

Values are mean ± SD, median (interquartile range) or n (%).* Post-hoc test with Bonferroni correction shows a p-value <0.05 between the Denver and the NY cohorts. † Post-hoc test with Bonferroni correction shows a p-value <0.05 between the Dutch and the NY cohorts. ‡ Post-hoc test with Bonferroni correction shows a p-value <0.05 between the Dutch and the Denver cohorts. § Of all PAH-CHD patients, separate from shunt types.

6MWD, six-minute walk distance; APAH-non-CHD, associated pulmonary arterial hypertension non congenital heart disease; BMI, body mass index; BNP, brain natriuretic peptide; IPAH/HPAH, idiopathic/hereditary PAH; mPAP, mean pulmonary arterial pressure; mPAP/mSAP, pulmonary-to-systemic arterial pressure ratio; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PAH-CHD, PAH associated with congenital heart disease; PVRi, pulmonary vascular resistance index; PVR/SVR, pulmonary-to-systemic vascular resistance ratio; Qpi, pulmonary blood flow index; Qp/Qs, pulmonary-to-systemic blood flow ratio; Qsi, systemic blood flow index; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVRi, systemic vascular resistance index; TcSO2, transcutaneous oxygen saturation; WU, Woods units.

Patients were comparable regarding age at diagnosis and sex. Time between first symptoms and diagnosis was significantly longer in the NY cohort than in the Dutch and Denver cohorts ($p<0.001$). In all 3 cohorts, most patients had diagnoses of IPAH/HPAH or PAH-CHD, although its distribution differed between the center cohorts. In the Dutch and NY cohorts, most patients had diagnoses of IPAH/HPAH versus PAH-CHD in the Denver cohort. The occurrence of APAH-non-CHD (including PAH associated with connective tissue disease, human immunodeficiency virus antibodies, hemolytic anemia, portal hypertension, drugs/toxins, pulmonary capillary hemangiomatosis, or pulmonary veno-occlusive disease) was higher in the Dutch cohort than in the NY cohort ($p=0.025$).

At time of diagnosis, patients in the Dutch cohort had higher WHO functional class, shorter 6-minute walk distance, higher PVRi and pulmonary-to-systemic vascular resistance ratio, and lower systemic blood flow index and mean systemic arterial pressure than the NY and Denver cohorts. Prevalence of acute responders depended on the criteria used, ranging from 14 to 19% of the NY patients, 15 to 31% of the Denver patients and 8 to 25% of the Dutch patients, and did not differ between the center cohorts.

Treatment

The 7-year cumulative treatment follow-up of the 3 center cohorts is plotted in Figure 1. The figure shows that in all 3 center cohorts, there were a similar, stable percentage of patients receiving CCB monotherapy. Considering PAH-targeted therapy, in all 3 cohorts, most patients started on monotherapy, with high percentages of patients on monotherapy within the first 3 years after diagnosis. In time, patients were switched from monotherapy to dual or triple therapy. In all 3 center cohorts a small number of patients received no PAH specific therapy within this 7-year period. These patients either died shortly after diagnosis before therapy could be started, received therapy after 7 years of follow-up, or received no therapy because their low WHO functional classification at that time did not warrant therapy according to evolving treatment strategies. Furthermore, the figure illustrates a higher mortality rate in the Dutch cohort and a higher percentage of patients lost to follow-up in the Denver and NY cohorts. The distribution of treatment strategy did not differ between the center cohorts (Table 2).

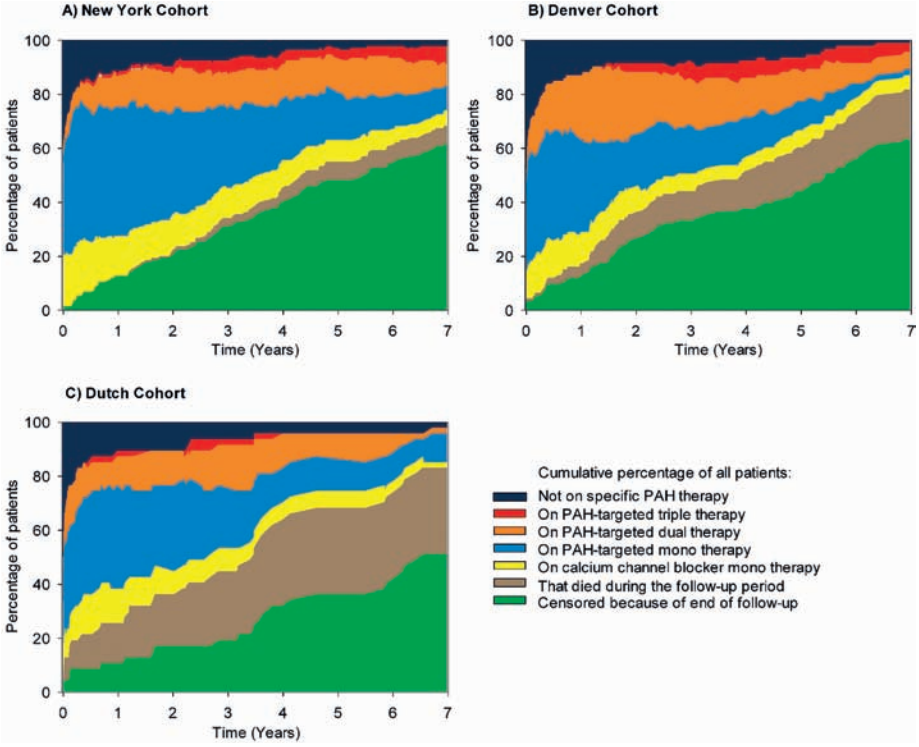

Figure 1. Real-time therapy per center cohort during a 7-year follow-up period
Real-time cumulative percentages of all patients per therapy group were plotted for the NY cohort (A), Denver cohort (B), and Dutch cohort (C). This plot shows the actual percent of patients in a specific therapy group, patients who died, and patients who were censored per follow-up time point. For example, 40% of the NY cohort at diagnosis (time point 0) did not receive any specific PAH therapy; after 1 year, 10% of this cohort received no specific PAH therapy; and after 5 years, 2% received no specific PAH therapy. Legend key is shown in the same descending order as in the figure. PAH, pulmonary arterial hypertension.

Table 2. Treatment strategy stratified by center cohort

Treatment strategy	All patients (N=272)	New York cohort (N=135)	Denver cohort (N=92)	Dutch cohort (N=45)	P-value
No specific PAH therapy	13 (5)	3 (2)	5 (5)	5 (11)	0.088
CCB monotherapy	24 (9)	11 (8)	10 (11)	3 (7)	
PAH-targeted monotherapy	96 (35)	44 (33)	34 (37)	18 (40)	
Without IV/SC prostanoids	76 (28)	31 (23)	32 (35)	13 (29)	
With IV/SC prostanoids	20 (7)	13 (10)	2 (2)	5 (11)	
PAH-targeted dual therapy	92 (34)	48 (36)	28 (30)	16 (36)	
Without IV/SC prostanoids	51 (19)	28 (21)	13 (14)	10 (22)	
With IV/SC prostanoids	41 (15)	20 (15)	15 (16)	6 (13)	
PAH-targeted triple therapy	47 (17)	29 (21)	15 (16)	3 (7)	
Without IV/SC prostanoids	14 (5)	10 (7)	3 (3)	1 (2)	
With IV/SC prostanoids	33 (12)	19 (14)	12 (13)	2 (4)	

Values are presented as n (%).
CCB, calcium channel blocker; IV, intravenous; PAH, pulmonary arterial hypertension; SC, subcutaneous.

Transplantation-free survival and predictors for prognosis

Follow-up time ranged from 0.01 to 13.7 years (median 4.0 years). During the study period, 7 NY patients (5%), 18 Denver patients (19%), and 15 Dutch patients (32%) died. Furthermore, 6 NY patients (4%) and 1 Dutch patient (2%) underwent lung transplantation. Overall, 1-, 3-, 5-, and 7-year transplantation-free survival rates were 96%, 89%, 81%, and 79%, respectively (Figure 2A). Unadjusted survival of children in the NY cohort was significantly more favorable than survival of patients in the other 2 cohorts (Figure 2B). Within the Dutch cohort, 33% of the deceased patients died within 3 months after diagnosis versus 6% and 0% of the deceased Denver and NY patients, respectively. Exclusion of these patients did diminish but not completely abolish the survival differences among the center cohorts (Figure 3A). Thirty-three NY patients (24%), 6 Denver patients (7%), and 2 Dutch patients (4%) were considered lost to follow-up according to the study methodology ($p<0.001$). In theory, such patients could favorably bias survival estimates because their potential death during the study period would not be taken into account. To illustrate the maximal effect, we estimated survival rates, hypothesizing that all such patients had died, regardless of any knowledge of these patients' health status after the end of the study period. In this worst-case scenario, no survival difference between the center cohorts was observed (Figure 3B).

Acute responders according to the Sitbon criteria had better survival than those who did not meet the Sitbon criteria ($p=0.029$). The Barst criteria and the REVEAL for childhood-onset PAH criteria did not differentiate between patients with better and worse survival in this population.

Univariate Cox regression analysis (Table 3) shows that compared to children with IPAH/HPAH, those with PAH-CHD had better transplantation-free survival, whereas those with APAH-non-CHD had worse survival. Furthermore, younger age at first symptoms, lower WHO functional class, lower systemic blood pressure, lower plasma N-terminal pro brain natriuretic peptide (NT-proBNP), lower mean right atrial pressure, higher systemic blood flow index, lower PVRi, and lower mPAP/mSAP were associated with better outcome. Sex, ethnicity, Down syndrome, age at diagnosis, syncope, 6-minute walk distance, z-scores for height and body mass index, plasma brain natriuretic peptide (BNP), and mean pulmonary arterial pressure were not associated with transplantation-free survival.

NT-proBNP and systolic and diastolic blood pressure were excluded from multivariate analysis because of >20% missing cases. Multivariate backward stepwise Cox regression analysis with the remaining variables that emerged from univariate analysis showed that diagnosis, WHO functional class, PVRi, mPAP/mSAP, and treatment strategy were the strongest independent predictors of transplantation-free survival (Table 4). To eliminate a potential effect of PAH-CHD patients with an open shunt for the value of these predictors, we repeated these analyses after exclusion of these 67 patients, which

did not change these findings. Also, the findings did not change when accounting for referral center.

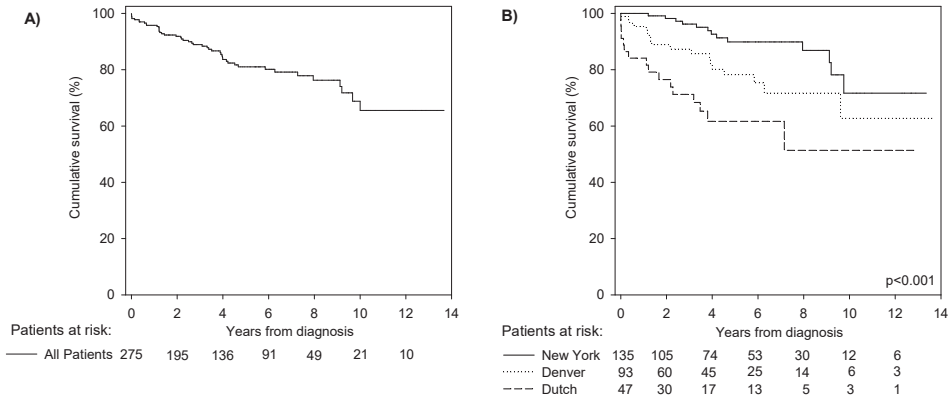

Figure 2. Survival of all included pediatric PAH patients and stratified by center cohort
Kaplan-Meier curves showing the survival (A) for all included pediatric PAH patients: 1-, 3-, 5-, and 7-year transplantation-free survival rates were 96%, 89%, 81%, and 79%, respectively. (B) For all patients stratified by center cohort. 1-, 3-, 5-, and 7-year survival rates were 100%, 96% 90%, and 90% for NY; 95%, 87%, 78%, and 72% for Denver; and 84%, 71%, 62%, and 62% for NL, respectively (p<0.001). Significant survival differences existed between all 3 center cohorts.

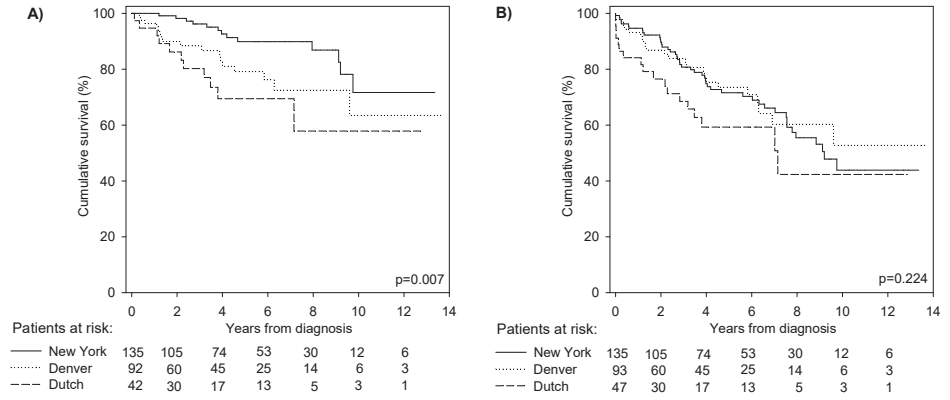

Figure 3. Survival of pediatric PAH patients adjusted for early death and lost to follow-up
Kaplan-Meier curves show the survival stratified by center cohort (A) after exclusion of all patients who died within 3 months after diagnosis. Significant survival differences between the NY cohort and the other two cohorts persists. (B) Assuming all patients lost to follow-up died. Now, no significant survival difference could be observed between the center cohorts.

Table 3. Patient, baseline clinical and hemodynamic characteristics associated with survival

	Univariate Cox regression analysis	
	Hazard ratio (95% CI)	P-value
Cohort		
New York	1.00	
Denver	2.356 (1.153 – 4.814)	0.019
Dutch	4.612 (2.215 – 9.602)	<0.001
Diagnosis		
IPAH/HPAH	1.00	
PAH-CHD	0.470 (0.228 – 0.966)	0.040
APAH-non-CHD	3.986 (1.798 – 8.836)	0.001
Age at first symptoms	1.080 (1.012 – 1.153)	0.020
WHO functional class III-IV versus I-II	2.231 (1.087 – 4.579)	0.029
Systolic blood pressure	1.030 (1.005 – 1.057)	0.020
Diastolic blood pressure	1.039 (1.005 – 1.075)	0.026
Log value of NT-proBNP	4.042 (1.173 – 13.926)	0.027
mRAP	1.107 (1.035 – 1.183)	0.003
Systemic blood flow index	0.734 (0.576 – 0.935)	0.012
PVRi	1.034 (1.011 – 1.057)	0.003
mPAP/mSAP*	1.133 (1.033 – 1.243)	0.008
Treatment strategy		
PAH-targeted monotherapy	1.00	
No specific PAH therapy	2.057 (0.828 – 5.108)	0.120
CCB monotherapy	0.121 (0.016 – 0.904)	0.040
PAH-targeted dual therapy	0.421 (0.203 – 0.874)	0.020
PAH-targeted triple therapy	0.401 (0.175 – 0.923)	0.032

* Hazard ratio per 0.1 change of mPAP/mSAP.

APAH-non-CHD, associated pulmonary arterial hypertension non-congenital heart disease; CCB, calcium channel blocker; CI, confidence interval; IPAH/HPAH, idiopathic/hereditary PAH; mPAP/mSAP, pulmonary-to-systemic arterial pressure ratio; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PAH-CHD, PAH associated with congenital heart disease; PVRi, pulmonary vascular resistance index; WHO, World Health Organization.

In the total population, during the study period, 5% of patients did not receive any PAH specific therapy, 9% of patients continued on CCB monotherapy, 35% of patients were treated with PAH-targeted monotherapy, and 34% and 17% were treated with dual and triple therapy, respectively (Table 2). Figure 4 shows survival rates stratified by treatment strategy. Patients' disease severity at diagnosis (defined by the identified predictors of survival) is shown in Tables 5 and 6. Patients receiving CCB monotherapy had significantly better hemodynamics than patients taking PAH-targeted therapy. Patients treated with dual and triple therapy during the study period had a diagnosis of PAH-CHD less frequently, higher mPAP/mSAP and tended to have higher WHO functional class and PVRi at diagnosis than patients who were treated with monotherapy. Patients who

Table 4. Multivariate backward stepwise Cox regression analysis of parameters associated with survival (N=196)

	Backward stepwise Cox regression analysis	
	Hazard ratio (95%CI)	P-value
Diagnosis		
IPAH/HPAH	1.00	
PAH-CHD	0.103 (0.027 – 0.396)	0.001
APAH-non-CHD	15.974 (4.402 – 57.960)	<0.001
WHO functional class III-IV versus I-II	3.251 (1.316 – 8.028)	0.011
PVRi	1.053 (1.017 – 1.090)	0.003
mPAP/mSAP*	1.282 (1.104 – 1.489)	0.001
Treatment strategy		
PAH-targeted monotherapy	1.00	
No specific PAH therapy†	19.311 (3.682 – 101.274)	<0.001
CCB monotherapy	0.385 (0.047 – 3.191)	0.377
PAH-targeted dual therapy	0.156 (0.057 – 0.422)	<0.001
PAH-targeted triple therapy	0.094 (0.029 – 0.302)	<0.001

* Hazard ratio per 0.1 change of mPAP/mSAP. † This 'non-treated' group consisted of patients clinically very well without therapy or who died rapidly after diagnosis before therapy could be started. In this statistical analysis, hazard ratio seems determined predominantly by the rapidly dying patients, not doing justice to the patients doing very well without treatment. Therefore this is regarded as not a meaningful hazard ratio. APAH-non-CHD, associated pulmonary arterial hypertension non congenital heart disease; CCB, calcium channel blocker; CI, confidence interval; IPAH/HPAH, idiopathic/hereditary PAH; mPAP/mSAP, pulmonary-to-systemic arterial pressure ratio; PAH-CHD, PAH associated with congenital heart disease; PVRi, pulmonary vascular resistance index; WHO, World Health Organization.

received IV/SC prostanoids had significantly higher WHO functional class and worse hemodynamics than patients who did not receive IV/SC prostanoids. Cox regression analysis indicated that dual and triple therapy treatments during the study period were associated with better survival than treatment with monotherapy. Although the non-use of PAH drugs was associated with worse survival compared to monotherapy in multivariate analysis, we consider the 'no therapy-group' not to be a meaningful control group for patients taking therapy, due to the composition of this group, including both patients with low WHO functional classes doing well without therapy and patients who died shortly after diagnosis.

In secondary sensitivity analyses, in which the robustness of the multivariate models was assessed in 3 different datasets, the variables mPAP/mSAP (78 to 89%), diagnosis (63 to 97%) and treatment strategy (50 to 95%) were selected in more than 50% of the models, whereas WHO functional class and PVRi were not.

Table 5. Predictors of outcome stratified by treatment strategy

			PAH-targeted therapy							
	CCB monotherapy		Monotherapy		Dual therapy		Triple therapy		P-value*	P-value†
	N	Value	N	Value	N	Value	N	Value		
Diagnosis	24		96		92		47		<0.001	0.164
IPAH/HPAH		17 (71)		31 (32)		52 (57)		37 (79)		
PAH-CHD		7 (29)		56 (58)		33 (36)		9 (19)		
APAH-non-CHD		0		9 (9)		7 (8)		1 (2)		
WHO functional class	21		74		89		40		0.078	0.271
I-II		13 (62)		44 (60)		40 (45)		16 (40)		
III-IV		8 (38)		30 (41)		49 (55)		24 (60)		
PVRi	24	8.73 ± 5.63	96	15.09 ± 10.99	92	16.84 ± 11.08	47	19.51 ± 9.27	0.068	<0.001
mPAP/mSAP	24	0.58 ± 0.21	94	0.80 ± 0.26	92	0.94 ± 0.27	47	0.95 ± 0.32	0.001	<0.001

Values are mean ± SD or n (%). * P-values for PAH-targeted mono vs. dual vs. triple therapy. † P-values for CCB mono therapy vs. PAH-targeted therapy.
APAH-non-CHD, associated pulmonary arterial hypertension non congenital heart disease; CCB, calcium channel blocker; IPAH/HPAH, idiopathic/hereditary PAH; mPAP/mSAP, pulmonary-to-systemic arterial pressure ratio; PAH-CHD, PAH associated with congenital heart disease; PVRi, pulmonary vascular resistance index; WHO, World Health Organization.

Table 6. Predictors of outcome stratified by the use of IV/SC prostanoids and PAH-targeted mono-, dual and triple therapy

	No IV/SC prostanoids used				IV/SC prostanoids used				
	Mono (N=76)	Dual (N=51)	Triple (N=14)	P-value*	Mono (N=20)	Dual (N=41)	Triple (N=33)	P-value*	P-value†
Diagnosis				<0.001				0.529	<0.001
IPAH/HPAH	18 (24)	20 (39)	12 (86)		13 (65)	32 (78)	25 (76)		
PAH-CHD	52 (68)	27 (53)	2 (14)		4 (20)	6 (15)	7 (21)		
APAH-non-CHD	6 (8)	4 (8)	0		3 (15)	3 (7)	1 (3)		
WHO functional class	(N=56)	(N=50)	(N=14)	0.134	(N=18)	(N=39)	(N=26)	0.251	<0.001
I-II	40 (71)	32 (64)	6 (43)		4 (22)	8 (21)	10 (39)		
III-IV	16 (29)	18 (36)	8 (57)		14 (79)	31 (80)	16 (62)		
PVRi	13.63 ± 10.66	15.38 ± 10.65	17.09 ± 7.79	0.421	20.64 ± 10.68	18.66 ± 11.47	20.54 ± 9.75	0.692	<0.001
mPAP/mSAP	0.75 ± 0.24	0.89 ± 0.23	0.94 ± 0.40	0.003	0.98 ± 0.23	0.99 ± 0.30	0.96 ± 0.30	0.843	<0.001

Values are mean ± SD or n (%). * P-values for PAH-targeted monotherapy versus dual versus triple therapy within the no IV/SC prostanoids used and the IV/SC prostanoids used groups. † P-values for no IV/SC prostanoids used vs. IV/SC prostanoids used.
Abbreviations as in Table 5.

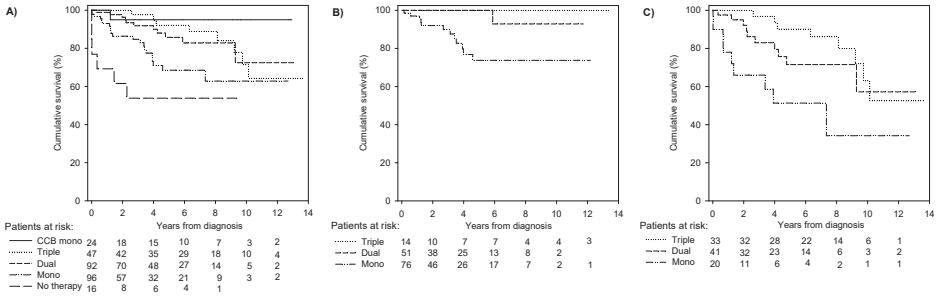

Figure 4. Survival of pediatric PAH patients stratified by treatment strategy
Kaplan-Meier curves show survival stratified by treatment strategy (A) for all patients; (B) for patients who did not receive intravenous/subcutaneous prostanoids; and (C) for patients who did receive intravenous/subcutaneous prostanoids. PAH, pulmonary arterial hypertension.

DISCUSSION

By direct comparison of contemporary patient cohorts from 3 major pediatric PAH referral centers, using standardized inclusion criteria, differences in unadjusted, transplantation-free survival rates were observed. However, adjustment for clinical and hemodynamic patient characteristics, which were identified as predictors of survival in the total cohort, resolved the survival differences among the center cohorts. Independent of these patient-related predictors, treatment with combination therapy with PAH-targeted drugs during the study period was associated with better survival than treatment with monotherapy with a PAH-targeted drug.

Parameters associated with survival

Children with APAH-non-CHD had significantly worse survival, whereas those with PAH-CHD showed favorable survival compared to IPAH/HPAH patients. This is congruent with several previous reports, although discrepant data have also been reported that show similar survival rates for pediatric PAH-CHD and IPAH/HPAH patients.[6,7,9,18] These reported discrepancies may be due to the heterogeneity of the heart defects that underlie PAH-CHD (e.g., closed versus open shunts, simple versus complex defects) for which survival rates may differ.[18] Further studies are needed on this issue.

WHO functional class is a non-invasive but subjective assessment of clinical condition that is widely used to predict outcome and guide therapy in adult PAH.[1,19] Its applicability in pediatric PAH has been debated as WHO functional class may be difficult to assess in infants and young children. However, various major referral centers for pediatric PAH have independently shown WHO functional class to be an important predictor of outcome, which was confirmed in the primary analysis in this study.[7-9,20] Secondary sensitivity analyses in the current study could not confirm the robustness of WHO func-

tional class as an independent predictor. This indicates that further studies, in addition to the current study, are needed to confirm the robustness of WHO functional class as independent predictor of outcome in pediatric PAH. A functional classification system customized for young children has been proposed but has yet to be validated.[21]

The hemodynamic parameters independently associated with survival in this study have previously been identified as predictors of outcome in other, mostly single-center studies.[7,10,22] Hemodynamic parameters have the advantages of objectivity and obtainability at any age. However, an important disadvantage is the need of a cardiac catheterization procedure, which often requires anesthesia or sedation in infants and young children with associated risks. In contrast to the Barst and REVEAL for childhood-onset PAH criteria, acute responders according to the Sitbon criteria had better survival than non-responders in this study, confirming previous reports.[22] Therefore, the Sitbon criteria seems to be applicable also in children and may better predict long-term survival in pediatric PAH.

In the current study, the natriuretic peptides BNP and NT-proBNP were available at diagnosis only for a small number of patients. We could not demonstrate an association between BNP and survival. However, despite low numbers, NT-proBNP was associated with survival, confirming previous reports.[9,23,24] Due to these low numbers, NT-proBNP could not be included in multivariate analysis, limiting its evaluation as an independent predictor. However, on the basis of the currently available literature, the authors feel that NT-proBNP should be part of the standardized follow-up for children with PAH and be included in future studies in order to adequately assess its value as an independent predictor of survival in pediatric PAH.

Other parameters, which have been previously reported to be associated with survival in pediatric PAH, such as age at diagnosis and z-score for height, were not associated with survival in the current study.[10,20]

Survival differences among the center cohorts

There were relatively more IPAH/HPAH and APAH-non-CHD patients in the Dutch cohort compared to the US cohorts, which attributed to the observed survival differences.

Based on WHO functional class and hemodynamics, children in the Dutch cohort appeared to have more severe disease than children in the US cohorts. Differences in the organization of care and referral patterns, in traveling distances and in accessibility to referral centers, may be factors that contribute to the Dutch cohort having an over-representation of the most severely ill patients. Such patients may not always reach the referral centers in the United States. Such factors could explain the observed difference in disease severity between the center cohorts.

Also, the proportion of patients lost to follow-up, which differed among the center cohorts, may attribute to the observed survival differences. In a hypothetical worst-case

scenario, where all patients lost to follow-up are assumed dead (obviously representing an overestimate of the number of deaths), a survival difference between the center cohorts could not be demonstrated.

Treatment patterns, as defined for this study (CCB monotherapy or PAH-targeted monotherapy, dual or triple therapy), did not differ between the center cohorts and, thus, did not contribute to the survival differences between the center cohorts.

Treatment

Our findings confirm that, like in adult PAH, in pediatric PAH a small select subgroup of patients (with favorable hemodynamics) has a favorable, long-term survival on CCB monotherapy without the need of additional PAH-targeted therapy.[25]

In this study, treatments with PAH-targeted dual and triple therapy during the study period were associated with better survival than treatment with PAH-targeted monotherapy, whether or not treatment strategy included IV/SC prostanoids. Differences in disease severity at diagnosis could not explain the observed survival differences among patients taking monotherapy or dual and triple therapy. Patients who received IV/SC prostanoid therapy had more severe disease at diagnosis. These data also illustrate that IV/SC prostanoids as monotherapy may not suffice in children with severe disease and is associated with poor outcome. Therefore, this study provides additional support for the notion of a more aggressive treatment approach in pediatric PAH, with the use of combination therapy. Given the relatively large proportion of patients receiving monotherapy found in all 3 center cohorts, there may be room for improvement in this respect. Whether an initial or an add-on treatment strategy would be most beneficial to improve outcome in pediatric PAH patients should be further evaluated.

A goal-oriented treatment strategy aiming at predefined improvement of the clinical condition instead of reacting to deterioration of the patient's clinical condition and leading to intensification of treatment has been suggested to improve outcome in adult PAH.[26,27] Such a strategy is likely to be beneficial also in pediatric PAH. However, in contrast to adult PAH, treatment goals to guide goal-oriented treatment are neither well defined nor validated in pediatric PAH.[12] The parameters identified to predict survival in this study may qualify for such treatment goals in the future. However, further research is essential to establish and validate treatment goals and to determine the effects of a goal-oriented treatment strategy on survival in this vulnerable patient population.

Study limitations

Retrospective studies come with certain limitations. However, the 3 center cohorts that were brought together come from 3 PAH-dedicated centers with standardized diagnostic and treatment protocols, minimizing these limitations. Multivariate analysis was limited by missing values within specific parameters that may be caused by either different

diagnostic and follow-up strategies among centers or by the inherent impossibility to obtain certain data in certain age or patient groups. In the analyses regarding treatment strategy, individual variations in doses and time relationships were not taken into account, precluding definitive conclusions on a causal relationship between treatment strategy and outcome. To address the risk of overfitting in this relatively small study, we performed secondary sensitivity analyses, in which the variables diagnosis, mPAP/mSAP, and treatment strategy were confirmed to be independent predictors of outcome, whereas WHO functional class and PVRi could not be confirmed in these secondary analyses, indicating that their robustness as independent predictors of outcome should be further studied. Diagnostic cardiac catheterizations were performed under both general anesthesia and conscious sedation. A potential effect of the mode of anesthesia on hemodynamics was not investigated in this study. Furthermore, the moderately high altitude of Denver was not taken into account in this study and may have negatively biased the outcome of the Denver cohort. Bringing together the complete consecutive patient cohorts of 3 major referral centers for pediatric PAH provided a unique opportunity to validate clinical patient characteristics that appeared to be responsible for observed survival differences and to find clues to optimize and guide therapy.

Conclusions

Unadjusted survival rates of pediatric PAH patients differed among 3 major referral centers. This study identified diagnosis, WHO functional class, mPAP/mSAP and PVRi as independent predictors of outcome that could explain the observed survival differences among the center cohorts. Moreover, we found that treatment with PAH-targeted combination therapy during the study period was independently associated with improved transplantation-free survival. Secondary sensitivity analyses indicated that the robustness of WHO functional class and PVRi as predictors of outcome in pediatric PAH deserves further evaluation.

REFERENCES

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. results from a national prospective registry. Ann Intern Med. 1991;115(5):343-349.
2. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
3. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.
4. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation. 2002;106(12):1477-1482.
5. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J. 2005;25(2):244-249.
6. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
7. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
8. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(4):697-704.
9. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
10. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
11. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S43-54.
12. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS), endorsed by the international society of heart and lung transplantation (ISHLT). Eur Heart J. 2009;30(20):2493-2537.
13. WHO Multicentre Growth Reference Study Group. WHO child growth standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006 (312 pages).
14. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-667.
15. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
16. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-3111.
17. Orford JL, Lennon R, Melby S, et al. Frequency and correlates of coronary stent thrombosis in the modern era: Analysis of a single center registry. J Am Coll Cardiol. 2002;40(9):1567-1572.
18. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.

19. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol. 2002;40(4):780-788.
20. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
21. Lammers AE, Adatia I, Cerro MJ, et al. Functional classification of pulmonary hypertension in children: Report from the PVRI pediatric taskforce, panama 2011. Pulm Circ. 2011;1(2):280-285.
22. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: Occurrence and prognostic value when comparing three response criteria. Eur Heart J. 2011;32(24):3137-3146.
23. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res. 2008;63(3):321-327.
24. Takatsuki S, Wagner BD, Ivy DD. B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide in pediatric patients with pulmonary arterial hypertension. Congenit Heart Dis. 2012;7(3):259-267.
25. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med. 1992;327(2):76-81.
26. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J. 2005;26(5):858-863.
27. Sitbon O, Galie N. Treat-to-target strategies in pulmonary arterial hypertension: The importance of using multiple goals. Eur Respir Rev. 2010;19(118):272-278.

8

Physical activity in pediatric pulmonary arterial hypertension measured by accelerometry: a candidate clinical endpoint

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ABSTRACT

Background– The development of evidence-based treatment guidelines for pediatric pulmonary arterial hypertension (PAH) is hampered by lack of pediatric clinical trials. Trial-design is hampered by lack of a feasible clinical endpoint in this population. We aimed to evaluate the use of accelerometry for measuring physical activity (PA) in pediatric PAH and to investigate its correlation with clinical disease severity markers.

Methods– We included children from the Dutch National Network for Pediatric Pulmonary Hypertension. Controls were recruited from the outpatient cardiology clinic of the Beatrix Children's Hospital. Children were asked to wear the accelerometer for 7 days. Vector magnitude counts per minute (VM CPM) and time per day spent in different PA intensity levels were defined as accelerometer outcomes.

Results– VM CPM was lower in children with PAH (n=29) than in controls (n=60) (647 vs. 921; $p<0.001$). Children with PAH spent less time in moderate and vigorous PA (13 vs. 29 minutes, 2 vs. 13 minutes per day; $p<0.001$). Time spent in moderate and vigorous PA correlated inversely with WHO functional class. Time spent in moderate PA correlated positively with 6-minute walk distance. In post hoc analyses, VM CPM and time spent in moderate/vigorous combined and vigorous PA were associated with outcome ($p\leq0.044$).

Conclusion– PA is markedly decreased in children with PAH. Accelerometer output correlated with clinical disease severity markers and may predict outcome. We showed an exciting potential of PA as meaningful endpoint for clinical trials in pediatric PAH, although its clinical utility and prognostic value needs to be further validated.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive disease of the small pulmonary arteries and has a poor prognosis. Randomized controlled trials (RCTs) have led to significant advances and the development of treatment guidelines for adult PAH, resulting in improved quality of life and survival in adults with PAH.[1]

In pediatric PAH, however, such advances are delayed and prognosis remains unfavourable.[2-5] In the United States none and in Europe only one of the currently available PAH-targeted drugs are approved for children. The development of evidence-based treatment guidelines is hampered by the lack of RCTs in the pediatric age group. One essential problem in the design of RCTs in pediatric PAH is the definition of validated clinically meaningful endpoints or surrogate endpoints applicable in the pediatric age spectrum.[6] Death may be considered a robust endpoint since improving survival is a main objective in the treatment of PAH. However, such an endpoint is associated with significant ethical and practical problems (including the need for long study duration and large sample size). Given the rareness and poor prognosis of (pediatric) PAH, mortality trials are neither feasible nor preferable.[7,8]

In adults, the 6-minute walk distance (6MWD) has served as primary endpoint in most pivotal clinical trials evaluating the efficacy of PAH-targeted drugs.[9-11] In children, its use has been debated since the test cannot be reliably performed in young children or in children with developmental delays. Currently reported data on the value of the 6MWD in pediatric PAH regarding the assessment of disease severity and prognosis are contradictory, which seems related to the selection of children.[2,12-14] To date no validated endpoints are available in young children with PAH and therefore this is a high unmet need.

Accelerometry has been proposed as a potential endpoint in pediatric PAH, also because its feasibility in young children.[8,15] It has been frequently used to measure physical activity (PA) in numerous clinical settings in both adults and children, including various cardiopulmonary diseases, and has been shown to correlate with peak oxygen consumption.[16-19] Recently, accelerometer output has been reported to correlate with measurements of exercise tolerance in adult PAH patients.[20,21]

To date, data regarding PA measured by accelerometry in children with PAH are lacking. In this study, we evaluated the value of accelerometry in pediatric PAH by comparing PA measured by accelerometry in children with PAH to that in healthy controls. Furthermore, we assessed whether accelerometer output correlates with disease severity and outcome in children with PAH.

METHODS

This is a prospective, observational study within the Dutch National Network for Pediatric Pulmonary Hypertension[22] and controls. The Medical Ethics Review Board of the University Medical Center Groningen waived the need for ethical approval. All subjects and/or their guardians gave written informed consent. In all included patients, PAH had been confirmed with cardiac catheterization and patients were classified according to the updated clinical classification of PAH, Nice, France, 2013.[23,24]

Patients and controls

Children with PAH who visited the outpatient clinic of the National Referral Center for Pulmonary Hypertension in Childhood between June 2013 and March 2016 were asked to wear the ActiGraph wGT3X accelerometer (Pensacola, Florida). Children with muscular diseases were excluded.

Patient characteristics, World Health Organization functional class (WHO-FC), 6MWD (in children ≥7 years of age) and serum levels of N-terminal pro brain natriuretic peptide (NT-proBNP) were assessed. The 6-minute walk test was conducted as previously reported.[12,25] Six-MWD was presented as both absolute values and percentage of predicted.[26] In one child with spondyloepiphyseal dysplasia the 6-minute walk test was regarded unreliable and therefore the test result was not used in the analyses. Data on medication use were also collected: calcium channel blocker monotherapy or PAH-targeted mono-, dual or triple therapy.

For every child with PAH, two controls matched by age and sex were recruited from children that visited the outpatient pediatric cardiology clinic of the Beatrix Children's Hospital for screening for cardiac diseases but appeared to have no, or not hemodynamically relevant, cardiac disease.

Accelerometry

Children were instructed to wear the accelerometer for 7 consecutive days on the right hip during all awake-time, except for water-related activities. The accelerometer was programmed to record triaxial data at a frequency of 60 Hertz. Data were processed using the ActiLife software (ActiGraph). Data were downloaded and integrated into 15 second epochs. Non-wear periods were defined as consecutive zero's for ≥90 minutes, with a two spike tolerance.[27] Days with ≥8 hours of accelerometer wear were considered valid. In infants who still slept during the day and consequently were awake for only 6-8 hours, days with ≥6 hours of accelerometer wear were considered valid. For inclusion in the analyses, patients were required to have ≥4 valid days.

Vector magnitude (VM) counts per minute (CPM) was defined as the primary accelerometer outcome. The VM is the square root of the quadrate of the three separate di-

mensional axes ($\sqrt{x^2+y^2+z^2}$). The total accelerometer VM counts were divided by the total number of minutes the device was worn to calculate VM CPM. PA intensity was defined as secondary accelerometer outcome and classified into sedentary, light, moderate and vigorous PA using cutpoints for the vertical axis as defined by Evenson et al.[28,29]

Statistics

Data are presented as mean (SD), median (interquartile range) or number (percentage). Statistical analysis was conducted using IBM SPSS 22.0 (Armonk, NY, USA) and R package (for partial Spearman correlation coefficients). Independent samples t-test, Mann Whitney U test, Chi square test or Fisher's exact test were used to compare data, as appropriate.

Pearson and Spearman correlation coefficients and linear regression analysis were used to evaluate the association between accelerometer output and clinical disease severity markers. For the sake of clinical interpretation, WHO-FC was taken as continuous variable in the linear regression analyses. Log transformation was performed for serum levels of NT-proBNP to achieve normality. Log-2 transformation was performed for combined moderate/vigorous, moderate and vigorous PA to achieve normality.

In post hoc outcome analyses, the first occurrence of death, lung transplantation or non-elective PAH-related hospitalization was defined as primary endpoint. Otherwise, children were censored at May 1st 2016. Freedom from events was depicted using a Kaplan-Meier curve. To explore whether accelerometer output predicted outcome, Cox regression analysis was performed. P-values of <0.05 were considered significant.

RESULTS

Children with PAH

In total, 30 children with PAH were asked to wear an accelerometer. One 7-year old child with Down syndrome refused to wear the accelerometer and was therefore excluded from the study.

Patient and disease characteristics of the remaining 29 children are shown in Table 1. There was a female predominance and median age at diagnosis was 3.1 years. Median time between diagnosis and accelerometer study was 2.9 years (IQR 0.9, 11.7 years). Four children (14%) were <5 years of age at the time of accelerometer study. Eight children (28%) wore the accelerometer within one year after diagnosis. Eleven children had idiopathic or hereditary PAH (IPAH/HPAH), 17 had PAH associated with congenital heart disease and one had PAH associated with connective tissue disease. Three children had Down syndrome. Most children were in WHO-FC II or III. Six-MWD was available in 19 children and not available in 9 children due to young age (<7 years; n=7) or due to devel-

opmental disorders (n=2). Two children received calcium channel blocker monotherapy and the remaining children received PAH-targeted therapies: 8 monotherapy, 15 dual therapy and 5 triple therapy.

Table 1. Patient and disease characteristics of the children with PAH

	All children with PAH (n=29)
Age of diagnosis (years)	3.1 (1.2, 9.7)
Female	19 (66)
Down syndrome	3 (10)
Diagnosis	
IPAH/HPAH	11 (38)
PAH-CHD	17 (59)
PAH-CTD	1 (3)
WHO-FC	
I	4 (14)
II	15 (52)
III	9 (31)
IV	1 (3)
6MWD* (meters; %pred)	411 ± 68; 61.6 ± 10.0
NT-proBNP** (ng/L)	160 (92, 350)
PAH therapy	
CCB monotherapy	2 (7)
PAH-targeted monotherapy	8 (27)
PAH-targeted dual therapy	15 (50)
PAH-targeted triple therapy	5 (17)

Data presented as median (interquartile range), number (percentage) or mean (standard deviation), as appropriate. *, 6MWD available for 19 children. **, NT-proBNP available for 28 children. %pred = percentage of predicted; 6MWD, 6-minute walking distance; CCB, calcium channel blocker IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension; NT-proBNP, N-terminal pro brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; WHO-FC, World Health Organization functional class.

Sixty age- and sex-matched controls were included (Table 2). Controls visited the outpatient pediatric cardiology clinic for evaluation of a cardiac murmur, palpitations or cardiac screening in the context of familial history of cardiomyopathy or arrythmia. Hemodynamic significant heart diseases were excluded in all. Diagnoses included no cardiac abnormality (n=57), trivial valve abnormalities (n=1) and hemodynamic not-relevant shunt-defects (small ventricular septal defect [n=1] and mini silent patent ductus arteriosus [n=1]).

Table 2. Physical activity of children with PAH and controls

	Children with PAH (n=29)	Controls (n=60)	P-value
Age at test (years)	12.0 (7.5, 14.7)	11.8 (9.0, 15.1)	0.878
Female	19 (66)	38 (63)	0.841
BMI (kg/m^2)	17.2 ± 2.6	18.0 ± 3.0	0.249
VM CPM	647 ± 274	921 ± 309	<0.001
Time in sedentary PA (hrs/day)	8.7 ± 2.0	8.3 ± 1.7	0.317
Time in light PA (hrs/day)	3.5 ± 1.3	3.8 ± 0.9	0.250
Time in MVPA (min/day)	13.3 (7.5; 25.0)	41.3 (31.9; 54.9)	<0.001
Time in moderate PA (min/day)	12.5 (4.8; 20.9)	29.2 (21.1; 38.5)	<0.001
Time in vigorous PA (min/day)	2.1 (0.8; 4.4)	13.4 (7.9; 19.4)	<0.001

Data presented as median (interquartile range), number (percentage) or mean (standard deviation), as appropriate. BMI, body mass index; hrs, hours; min, minutes; MVPA, combined moderate/vigorous physical activity; PA, physical activity; VM CPM, vector magnitude counts per minute.

Physical activity in children with PAH and controls

All included children wore the accelerometer for ≥4 valid days and were included in the PA analyses. The majority of these children (89%) had six or seven valid days, which did not differ between children with PAH and controls (p=0.642). Mean wear time per valid day was 12.5 ± 1.7 hours for children with PAH and 12.8 ± 1.1 hours for controls (p=0.318). There was no significant day-to-day variance in VM CPM (paired samples t-tests; p≥0.094). During the weekend, children wore the accelerometer for a shorter time per day compared to week days (12.0 ± 1.6 hours vs. 13.0 ± 1.4 hours per day; p<0.001). However, no significant difference in VM CPM during week or weekend days could be demonstrated (paired samples t-test; p=0.641).

Mean VM CPM was significantly lower in the children with PAH compared to controls (Table 2, Figure 1). Furthermore, children with PAH spent significantly less time per day in both moderate and vigorous activities compared to controls (Table 2, Figure 2).

Accelerometer output in pediatric PAH

Mean VM CPM did not differ between the 3 children with and the 26 children without Down syndrome (733 vs. 638, p=0.574). There was a significant correlation between age and VM CPM (r=-0.495, p=0.006), and a considerable stronger correlation between age and time spent in sedentary (r=0.764, p<0.001) and light PA (r=-0.466, p=0.011). Time spent in moderate, vigorous and combined moderate/vigorous PA did not correlate with age (data not shown). Children with associated PAH spent less time in vigorous PA than children with IPAH/HPAH (r=-0.421, p=0.023 [reference category IPAH/HPAH]). We could not demonstrate a correlation between accelerometer output and sex, BMI, diagnosis or NT-proBNP serum level (data not shown).

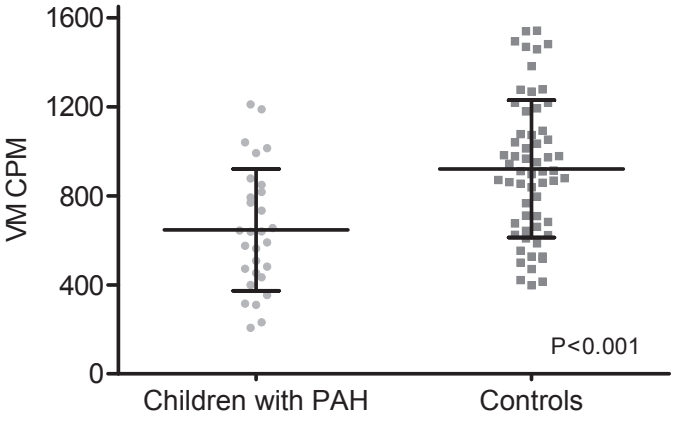

Figure 1. VM CPM for the children with PAH and controls
Showing all individual data for each group with mean and standard deviation. Mean VM CPM was significantly lower in the children with PAH compared to controls (647 vs. 921 CPM respectively, p<0.001).

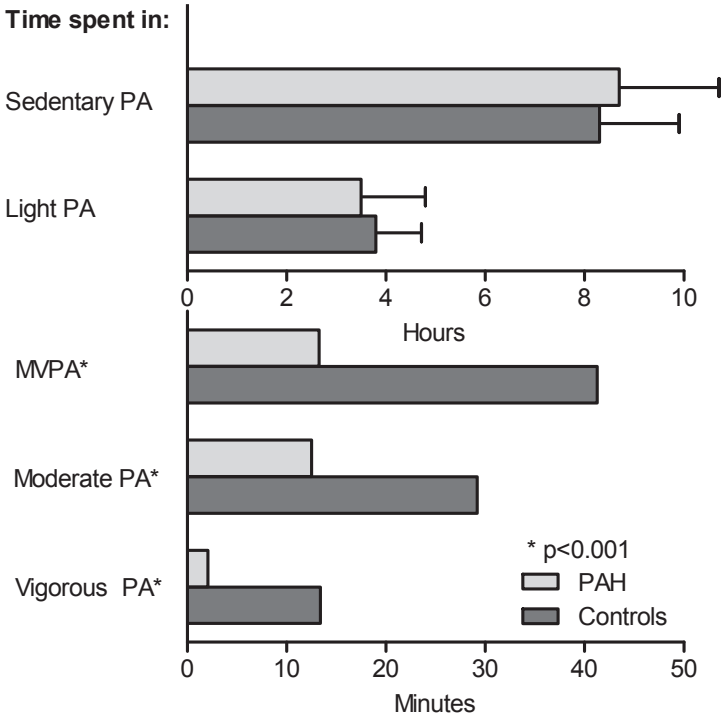

Figure 2. Physical activity intensity levels for the children with PAH and controls
Showing mean and standard deviations of hours per day spent in sedentary and light physical activity (PA) and median minutes per day spent in moderate/vigorous PA (IQR children with PAH: 7.5, 25.0, controls: 31.9, 54.9), moderate PA (IQR children with PAH: 4.8, 20.9, controls: 21.1, 38.5) and vigorous PA (IQR children with PAH: 0.8, 4.4, controls: 7.9, 19.4) for the children with PAH and controls. * represents a p-value <0.001. MVPA, moderate/vigorous physical activity; PA, physical activity.

Table 3. Correlations of clinical disease severity markers and accelerometer output

	WHO functional class				6MWD			
	Univariate		Adjusted for age and diagnosis		Univariate		Adjusted for age and diagnosis	
	r	P-value	r	P-value	r	P-value	r	P-value
VM CPM	-0.369	0.049	-0.266	0.233	0.221	0.363		
Sedentary PA	0.269	0.119			0.002	0.993		
Light PA	-0.282	0.138			0.282	0.242		
MVPA	-0.398	0.002	-0.380	0.053	0.521	0.022	0.429	0.085
Moderate PA	-0.371	0.048	-0.356	0.085	0.585	0.009	0.530	0.029
Vigorous PA	-0.466	0.015	-0.445	0.022	0.456	0.050	0.317	0.215

Data presented as correlation coefficients, r. 6MWD, 6-minute walking distance; MVPA, combined moderate/vigorous physical activity; PA, physical activity; VM CPM, vector magnitude counts per minute; World Health Organization functional class.

VM CPM correlated inversely with WHO-FC in univariate analysis but lost its significance when corrected for age and diagnosis (Table 3). Time spent in moderate, vigorous and combined moderate/vigorous PA correlated inversely with WHO-FC, which did not change substantially after adjustment for age and diagnosis. Time spent in moderate, vigorous and combined moderate/vigorous PA correlated positively with 6MWD, although with respect to time spent in vigorous PA statistical significance did not remain after adjustment for age and diagnosis. We also tested for differences in regression coefficients between accelerometer outcomes and clinical disease severity markers in univariate and adjusted for age and diagnosis analysis (Table 4). The findings remained generally the same. In addition, similar correlation and regression coefficients were observed between the percentage of predicted 6MWD and time spent in moderate, vigorous and combined moderate/vigorous PA.

Outcome

During a median follow-up of 2.2 years, 3 children were non-electively hospitalized for PAH-related reasons, i.e. progressive right heart failure. Two children subsequently died within weeks after admission. In none of the 29 children intravenous or subcutaneous prostanoids were initiated during the study period.

Post hoc Cox regression analysis revealed that lower VM CPM was significantly associated with a shorter time to event (Figure 3). Also less time spent in more intense activity levels (combined moderate/vigorous PA or vigorous PA) was associated with worse outcome (p=0.036 and p=0.044, respectively).

Table 4. Regression coefficients of accelerometer outcomes and clinical disease severity markers

	Univariable		Adjusted for age and diagnosis	
Predictive value of:	B [95% CI]	P-value	B [95% CI]	P-value
VM CPM for:				
WHO-FC	-0.1 [-0.2 to 0.0]	0.065	-0.1 [-0.2 to 0.1]	0.314
6MWD (meters)	6 [-8 to 21]	0.363	7 [-12 to 26]	0.442
Sedentary PA (hrs/day) for:				
WHO-FC	0.1 [0.0 to 0.2]	0.121	0.0 [-0.2 to 0.2]	0.771
6MWD (meters)	0 [-18 to 19]	0.993	3 [-23 to 28]	0.835
Light PA (hrs/day) for:				
WHO-FC	-0.2 [-0.4 to 0.0]	0.075	-0.12 [-0.4 to 0.1]	0.229
6MWD (meters)	17 [-13 to 48]	0.242	32 [0 to 64]	0.050
MVPA (min/day) for:				
WHO-FC	-0.2 [-0.4 to 0.0]	0.038	-0.2 [-0.4 to 0.0]	0.040
6MWD (meters)	24 [4 to 44]	0.022	20 [-3 to 44]	0.085
Moderate PA (min/day) for:				
WHO-FC	-0.2 [-0.4 to 0.02]	0.047	-0.2 [-0.4 to 0.0]	0.062
6MWD (meters)	29 [8 to 49]	0.009	26 [3 to 48]	0.029
Vigorous PA (min/day) for:				
WHO-FC	-0.2 [-0.3 to 0.0]	0.038	-0.2 [-0.3 to 0.0]	0.026
6MWD (meters)	17 [0 to 34]	0.050	13 [-9 to 35]	0.215

Data presented as B with 95% confidence intervals. B represents the increase or decrease in WHO-FC or 6MWD per 100 increase in VM CPM, hours per day spent in sedentary and light PA and per doubling of minutes per day spent in MVPA, moderate or vigorous PA. 6MWD, 6-minute walking distance; MVPA, combined moderate/vigorous physical activity; PA, physical activity; hrs, hours; min, minutes; VM CPM, vector magnitude counts per minute; World Health Organization functional class.

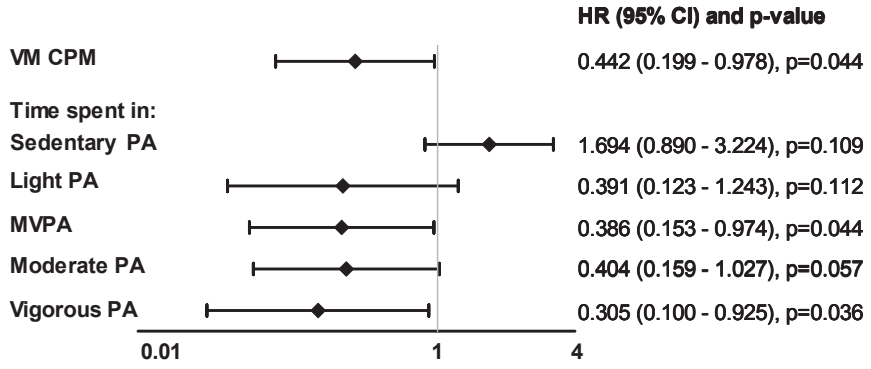

Figure 3. Predictive value of accelerometer outcomes for freedom of events
Forest plot showing hazard ratios with 95% confidence intervals. Hazard ratios per 100 increase in VM CPM, hours per day spent in sedentary and light PA and per doubling of minutes per day spent in MVPA, moderate or vigorous PA. Event was defined as non-elective PAH-related hospitalization, lung transplantation or death. CI, confidence interval; HR, hazard ratio; MVPA, combined moderate/vigorous physical activity; PA, physical activity; VM CPM, vector magnitude counts per minute.

DISCUSSION

This study is the first to demonstrate that PA measured by accelerometry is markedly decreased in children with PAH compared to controls, particularly moderate and vigorous PA. Furthermore, accelerometer output correlated considerably with clinical disease severity markers and outcome.

Accelerometry in pediatric PAH

In pediatric PAH, there is a high unmet need for an endpoint or a validated surrogate endpoint applicable in the pediatric age spectrum. A clinically meaningful endpoint should reflect how a patient feels, functions or survives.[30] Function refers to the ability of a patient to carry out normal daily activities. This is especially important in PAH as exercise intolerance, reflected by dyspnea at exertion, increased WHO-FC and impaired 6MWD and peak oxygen consumption, is one of the main features of PAH.[1,5,23,31] Children with PAH cannot keep up with their peers in participating in the normal daily activities of childhood, such as playing in the playground, running, dancing or playing soccer, which greatly affects quality of life. In this study, we used accelerometry to objectively measure PA, and confirmed that PA is significantly decreased in children with PAH. As such, accelerometer output provides direct information on how a child with PAH functions. In this respect, accelerometer output is thus not a surrogate endpoint, with inherently required validation criteria, but constitutes a clinically meaningful endpoint.

Impaired exercise tolerance in PAH has been usually evaluated using 6MWD. Recently, a study in the Dutch cohort of pediatric PAH patients, showed that the 6MWD is an independent predictor of prognosis in children ≥7 years of age and reflects disease severity and exercise tolerance in daily life.[12] The current study demonstrates that accelerometer output correlates with 6MWD, confirming the clinical relevance of this measurement. This correlation has also been reported in adults with PAH.[20,21] A well-established limitation of the 6-minute walk test is that it cannot be reliably performed in young children or in children with severe mental or physical disabilities. Furthermore, it can be influenced by non-PAH related factors such as motivation of the child and guidance during the test. In contrast, accelerometry provides an objective measurement of PA and can be reliably performed in children of all ages regardless of any disabilities. Therefore, accelerometry could be a good alternative to evaluate exercise tolerance in children who cannot (reliably) perform a 6-minute walk test.

Another well-established clinical parameter for disease severity is the WHO-FC, a subjective assessment of a patient's clinical condition using the occurrence of symptoms at different levels of PA. Its value in infants and young children has been debated as it is based on the observation and impression of caregivers and/or the treating physician. Nevertheless, WHO-FC has been shown to be a strong and independent predictor of

prognosis also in pediatric PAH.[13,32] Also, changes in WHO-FC were recently shown to predict survival.[33] In this study, accelerometer output correlated with WHO-FC which further supports the value of accelerometry in assessing exercise tolerance in pediatric PAH.

In this cross-sectional study, accelerometer output did not correlate with single time-point measurements of NT-proBNP serum level. Although single time-point measurements of NT-proBNP have been shown to predict outcome in pediatric PAH, its major strength is that changes in NT-proBNP serum levels during follow-up predict (changes in) outcome.[33] As such, NT-proBNP qualifies as a surrogate endpoint and may serve as a treatment goal in pediatric PAH. Accelerometer output, however, reflecting how a patient feels and functions, constitutes a clinically meaningful endpoint in itself. Although both measurements are affected by the disease PAH and both may predict outcome in pediatric PAH, they represent two different features of PAH, i.e. myocardial load versus stamina and it is not clear whether the mechanisms by which both measurements are affected by the disease are the same. This also accounts for other proposed endpoints, including biomarkers, echocardiographic parameters and hemodynamics. Therefore, the absence of a one-on-one correlation between accelerometer output and such endpoints does not diminish the value of either of them nor of accelerometry as clinically meaningful endpoint in pediatric PAH. Further research is needed to establish whether changes in NT-proBNP serum levels over time correlate with changes in accelerometer output.

A major advantage of accelerometry over these other proposed endpoints, is that it is a direct, objective, non-invasive and relatively cheap measurement. Furthermore, accelerometry appeared to be feasible in children of all ages. Out of 30 children, in only one child with Down syndrome accelerometry appeared not feasible due to non-compliance. Biomarkers, echocardiographic parameters and hemodynamics do not directly reflect how a patient feels, functions or survives. However, these measurements may carry prognostic value and could qualify as surrogates for outcome.[7,34] To date, their use as surrogates remains to be validated. In addition, the assessment of hemodynamics requires the need for invasive measurement, as these are obtained during cardiac catheterization, bringing along certain risks and often the need for sedation or anaesthesia.[35,36]

In a post hoc analysis, accelerometer output predicted outcome, defined as the first occurrence of death, lung transplantation or hospitalization. It must be noted that only three events occurred and all consisted of non-elective PAH-related hospitalizations. Reason for hospitalization was progressive right heart failure and two children died within weeks after hospitalization. Although these results suggest that accelerometer output is of prognostic value in pediatric PAH, this study does not allow for definitive

conclusions in this respect. Further research is needed to further establish the value of accelerometry as prognostic tool.

PA in children with PAH

There may be various explanations for the markedly decreased PA in children with PAH. First, the PAH itself, resulting in decreased cardiac output, could very well cause the exercise intolerance resulting in decreased PA. Children with associated PAH spent even less time in vigorous PA than children with IPAH/HPAH. This group mostly included children with PAH-CHD and shunt-defects (n=14). Such children may not be able to reach a vigorous PA intensity level due to cyanosis that develops or aggravates during exercise. Secondly, it may be that PA is restricted by the caregivers/parents (or the children with PAH themselves) due to concerns and fear for adverse effects of PA, such as dyspnea, syncope or sudden death. Chronic restriction of PA will lead to decreased fitness and decreased muscle strength. The latter was recently shown in adult PAH patients.[37] Such fears might have been enhanced by the fact that exercise training, i.e. moderate or vigorous PA, has long been believed to be harmful in patients with PAH.[38] However, this point of view is changing and, with the improved therapeutic options for PAH, exercise training is nowadays regarded to be safe.[1] Moreover, several studies in adults with PH showed that exercise training improved exercise capacity, 6MWD, WHO-FC, quality of life and peak oxygen consumption and led to higher levels of PA (measured by questionnaires) and decreased levels of fatigue.[39-41] Future research, aiming at improving quality of life, could be directed towards evaluating muscle strength and the value of exercise programs also in pediatric PAH. Accelerometry could be used as a tool to guide such programs and monitor efficacy.

Strengths, limitations and future directions

As validated endpoints are currently lacking in pediatric PAH, the results of this proof of concept study forms an important base for the validation of accelerometer output as a clinically meaningful endpoint. Nevertheless, further validation of this potentially valuable endpoint is warranted. Its use should be evaluated in a second, larger cohort preferably including a larger proportion of younger children and infants. However, it appears an extreme challenge to include young children with PAH in current clinical trials and, in this context, the current proportion of 14% children <5 years of age is satisfactory. Accelerometry has been previously validated in young children in other conditions supporting its use also in the very young ones.[18] A potential disadvantage of the use of accelerometry in infants children may be that accelerometry cannot recognize when a child is carried by a caregiver. The use of diaries may overcome this limitation. The age distribution in our cohort, with predominantly patients older than 5 years of age, did allow for comparisons between accelerometer output and 6MWD.

Further aspects that need to be addressed in order to validate the use of accelerometry in pediatric PAH include investigating how PA levels measured by accelerometry change over time in this population, whether therapy effects can be detected and the determination of a minimal clinically important change in PA. With respect to reproducibility, the accelerometer device used in the current study has been shown to have a good reproducibility in children, also in preschool children.[42,43] While in the current study accelerometer output did not differ between week- and weekend days, it has been suggested that children are less active in the weekends than during weekdays.[44] Also, there may be seasonal variation in children's physical activity.[45] These remain topics for further investigation.

The children with PAH included in this study come from a national cohort with standardized diagnostic, follow-up and treatment protocols. The inclusion of a matched control group provided the opportunity to directly compare PA between children with PAH and children without PAH. Complete and standardized follow-up in all children further enhanced the power of this study. In this study, we used the Evenson cutpoints for PA intensity levels, currently recommended to be used in children and adolescents.[29] General consensus on such cutpoints is still to be achieved. The relatively small sample size is a limitation of this study but inherent to prospective studies in a rare disease as pediatric PAH.

Conclusion

Physical activity can be assessed objectively in children of various ages using accelerometry. Children with PAH have markedly decreased PA compared to healthy controls. Especially time spent in higher PA intensity levels was severely reduced. Accelerometer output is associated with clinical disease severity independent from age and diagnosis and may also predict outcome. It provides an objective and direct measurement of how a patient functions. Therefore, accelerometer output could serve as a clinically meaningful endpoint for clinical trials in children with PAH. Further validation in a second, larger population of children with PAH is warranted.

REFERENCES

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS): Endorsed by: Association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
2. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63(20):2159-2169.
3. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
4. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
5. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
6. Berger RM. Pulmonary hypertension: Smaller kids, smaller steps. Lancet Respir Med. 2014;2(5):348-350.
7. Gomberg-Maitland M, Bull TM, Saggar R, et al. New trial designs and potential therapies for pulmonary artery hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D82-91.
8. Adatia I, Haworth SG, Wegner M, et al. Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee. Pulm Circ. 2013;3(1):252-266.
9. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165(6):800-804.
10. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896-903.
11. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148-2157.
12. Douwes JM, Hegeman AK, van der Krieke MB, Roofthooft MT, Hillege HL, Berger RM. Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hypertension. Int J Cardiol. 2016;202:34-39.
13. Ploegstra MJ, Zijlstra WM, Douwes JM, Hillege HL, Berger RM. Prognostic factors in pediatric pulmonary arterial hypertension: A systematic review and meta-analysis. Int J Cardiol. 2015;184:198-207.
14. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. Int J Cardiol. 2010;142(2):159-165.
15. European Medicines Agency: EMA/CHMP/213972/2010. Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500122492.pdf; June, 2016.
16. Muller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. Eur Heart J. 2009;30(23):2915-2920.

17. Plasqui G, Bonomi AG, Westerterp KR. Daily physical activity assessment with accelerometers: New insights and validation studies. Obes Rev. 2013;14(6):451-462.
18. Borkhoff CM, Heale LD, Anderson LN, et al. Objectively measured physical activity of young canadian children using accelerometry. Appl Physiol Nutr Metab. 2015;40(12):1302-1308.
19. Savi D, Di Paolo M, Simmonds N, et al. Relationship between daily physical activity and aerobic fitness in adults with cystic fibrosis. BMC Pulm Med. 2015;15:59-015-0036-9.
20. Mainguy V, Provencher S, Maltais F, Malenfant S, Saey D. Assessment of daily life physical activities in pulmonary arterial hypertension. PLoS One. 2011;6(11):e27993.
21. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. Chest. 2012.
22. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: Complex presentation and diagnosis. J Pediatr. 2009;155(2):176-82.e1.
23. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
24. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
25. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-117.
26. Geiger R, Strasak A, Treml B, et al. Six-minute walk test in children and adolescents. J Pediatr. 2007;150(4):395-9, 399.e1-2.
27. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc. 2011;43(2):357-364.
28. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci. 2008;26(14):1557-1565.
29. Trost SG, Loprinzi PD, Moore R, Pfeiffer KA. Comparison of accelerometer cut points for predicting activity intensity in youth. Med Sci Sports Exerc. 2011;43(7):1360-1368.
30. Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. Clinical measurement in drug evaluation. New York: J. Wiley; 1995:3-22.
31. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child. 2011;96(2):141-147.
32. del Cerro Marin MJ, Sabate Rotes A, Rodriguez Ogando A, et al. Assessing pulmonary hypertensive vascular disease in childhood. data from the spanish registry. Am J Respir Crit Care Med. 2014;190(12):1421-1429.
33. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J. 2014;44(6):1616-1626.
34. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med. 2012;31(25):2973-2984.
35. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MR. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. Br J Anaesth. 2007;98(5):657-661.
36. Beghetti M, Schulze-Neick I, Berger RM, et al. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the global TOPP registry (tracking outcomes and practice in paediatric pulmonary hypertension). Int J Cardiol. 2016;203:325-330.

37. Breda AP, Pereira de Albuquerque AL, Jardim C, et al. Skeletal muscle abnormalities in pulmonary arterial hypertension. PLoS One. 2014;9(12):e114101.
38. Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet. 1998;352(9129):719-725.
39. Chan L, Chin LM, Kennedy M, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. Chest. 2013;143(2):333-343.
40. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114(14):1482-1489.
41. Weinstein AA, Chin LM, Keyser RE, et al. Effect of aerobic exercise training on fatigue and physical activity in patients with pulmonary arterial hypertension. Respir Med. 2013;107(5):778-784.
42. De Vries SI, Van Hirtum HW, Bakker I, Hopman-Rock M, Hirasing RA, Van Mechelen W. Validity and reproducibility of motion sensors in youth: A systematic update. Med Sci Sports Exerc. 2009;41(4):818-827.
43. Baque E, Barber L, Sakzewski L, Boyd RN. Reproducibility in measuring physical activity in children and adolescents with an acquired brain injury. Brain Injury. 2016:1-7.
44. Nilsson A, Anderssen SA, Andersen LB, et al. Between- and within-day variability in physical activity and inactivity in 9- and 15-year-old european children. Scand J Med Sci Sports. 2009;19(1):10-18.
45. Mattocks C, Leary S, Ness A, et al. Intraindividual variation of objectively measured physical activity in children. Med Sci Sports Exerc. 2007;39(4):622-629.

9

General discussion

In the past decades, there have been major advances in unraveling the pathophysiology and –biology of pulmonary arterial hypertension (PAH), its classification and treatment options. The introduction of the PAH-targeted drugs and implementation of evidence-based treatment guidelines have strongly improved quality of life and survival in adults with PAH. Unfortunately, due to several unique features of pediatric PAH, including the frequent occurrence of genetic or congenital anomalies and the influence of growth and developmental issues on disease progression, outcome and pharmacokinetics and –dynamics, adult data cannot be simply extrapolated to children with PAH. Data in pediatric PAH remain scarce. The aims of this thesis were to provide more insights and knowledge towards optimal classification, treatment strategies and outcome by characterizing the subgroup of pediatric PAH associated with congenital heart disease (PAH-CHD) and assessing the value of the Nice congenital heart disease classification (Nice-CHD-classification), by describing current treatments and treatment strategies and their effect on outcome, by describing survival and its predictors in children with PAH in the current era of PAH-targeted drugs, and by evaluating the value a potential clinical endpoint for pediatric randomized controlled trials (RCTs). In this chapter, the main findings of this thesis will be discussed including directions for future research.

TOWARDS OPTIMAL CLASSIFICATION IN PEDIATRIC PAH

Pulmonary hypertension (PH) is a symptom of a heterogeneous spectrum of diseases with various pathological, pathophysiological, clinical and therapeutic differences. During the 2nd World Symposium on PH (Evian, France, 1998) a clinical classification for PH consisting of five major subgroups based on pathological, pathophysiological, clinical and therapeutic similarities was presented for the first time. Since then, this classification has been modified several times according to evolving insights and was last updated during the 5th World Symposium on PH in Nice, France, 2013 (Nice classification).[1] During this World Symposium, a pediatric task force was included for the first time. Ideally, a classification system could be used to predict pace and risk of disease progression and to determine the optimal treatment strategy for each individual patient.

In pediatric PAH, idiopathic PAH (IPAH) and PAH-CHD are most common.[2-4] Other forms of PAH are less common[2-4], which is confirmed by the small part (6%) of children with associated PAH other than CHD in the cohort presented in Chapter 7. In this cohort, we showed that children with PAH-CHD had better and children with associated PAH other than CHD had worse survival compared to children with IPAH, independent from patient characteristics and disease severity. Data on whether survival of children with PAH-CHD is indeed favorable compared to that of children with IPAH are contradictory.[2,5,6] Several studies report favorable survival of children with PAH-CHD, whereas others report

similar, or at least not favorable, survival of this group compared to IPAH.[2,5,6] A major reason for this discrepancy is the fact that PAH-CHD comprises a heterogeneous group of patients, especially in children. The broad variety in CHD and extracardiac comorbidities plays an important role in this heterogeneity.[7] Furthermore, in the past, not all CHD have been strictly classified as PAH-CHD. For instance, CHD regarded not sufficient to explain the development of childhood PAH has often been classified as IPAH, or IPAH-like. Thus, different classification and inclusion criteria in studies could have led to different study populations impeding definitive conclusions regarding expected disease course, response to therapy and outcome in different subtypes of pediatric PAH.

Since the updated clinical classification of PH in 2009, it has been proposed to further classify PAH-CHD into Eisenmenger syndrome, PAH associated with left-to-right shunt, PAH with coincidental CHD and post-operative PAH (Nice-CHD-classification).[1,8] Although this classification has been shown to identify differences in patient and disease characteristics and survival in adults[9], data in pediatric PAH were lacking. We report in Chapter 2 that a conventional shunt-based classification and the new Nice-CHD-classification identify groups with specific patient and disease characteristics in pediatric PAH. Therefore, these classifications may be useful in children as well. However, an important limitation of these classifications is that there is no place for non-shunt CHD which forms a substantial part (10-15%) of pediatric PAH-CHD. In our cohort, non-shunt CHD included aortic coarctation, repaired total anomalous pulmonary venous return, unilateral absence of a pulmonary artery, Scimitar syndrome and transposition of the great arteries (TGA) repaired with arterial switch operation (ASO) in the neonatal period. Non-shunt CHD certainly deserves and requires a place in any optimal classification, as the PAH severely worsens prognosis also in these patients. Recently, a clinical classification system specifically for pediatric PAH was proposed, the Panama classification.[10] The Panama classification aims to comprise the complete spectrum of childhood PH and consists of 10 major categories and more than 100 subgroups. One category includes 'pediatric heart disease', which in itself consists of more than 15 subcategories. Consequently, all non-shunt CHD have a place in this classification, mostly in the 'pediatric heart disease' category. However, this many subgroups will lead to very small numbers in each group, especially in a rare disease as pediatric PAH, hampering the purpose of risk stratification and tailored treatment approaches. Therefore, a balance between being all-inclusive and adequate simplicity is key in an optimal classification.[11] Future efforts should be directed towards further refinement of the Nice-CHD-classification in order to provide a home for the complete spectrum of CHD associated with childhood PAH including non-shunt CHD.

The subgroup of PAH after neonatal ASO for TGA is of particular interest as this concurrence is a well recognized clinical entity in pediatric PH centers. However, a clinical characterization of this entity was lacking. In Chapter 3 we present an international

cohort of 25 children with PAH after neonatal ASO for TGA. We estimate the reported incidence of this association to be 0.6-1.0% of children who undergo neonatal ASO for TGA. Hemodynamic abnormalities very early in life, either pre- or perinatally, may play an important role in the development of PAH in these children.[12] That hemodynamics early in life may form an important determinant in the development and course of childhood PAH is also illustrated by children with so-called 'accelerated' PAH.[3] Children with an unrepaired non-restrictive post-tricuspid shunt-defect, such as a ventricular septal defect, normally develop PAH in the first years of life with a gradual increase in pulmonary vascular resistance, eventually resulting in reversal of the shunt and Eisenmenger syndrome.[13] However, in Chapter 2 we report three children that presented with Eisenmenger physiology already in the first half year after birth and all died. Such children with 'accelerated' PAH have been previously reported to have very poor prognosis.[3] In these children, the pulmonary vascular bed may not adapt normally to postnatal life which may lead to severe persistent pulmonary hypertension of the newborn and/or advanced PAH early in life.

A unique feature of pediatric PAH is the fact that organs and tissues in fetal life and early childhood are developing and maturing. Developmental, genetic or congenital anomalies may hamper or alter normal organ development/maturing, which could lead to perinatal maladaptation and pulmonary vascular disease early in life. Furthermore, prenatal pathological or environmental insults may harm the growing lung which could lead to underdevelopment of the pulmonary vasculature or pulmonary hypoplasia.[10,11,14] As such, these factors may play a modifying role in the development and progression of PAH[10,11,14], which indeed seems to be the case in the abovementioned subgroups of PAH-CHD. In contrast to the Panama classification, the role of such developmental or maladaptive factors in pediatric PAH, including altered pre- and perinatally hemodynamics, is currently insufficiently acknowledged in the Nice(-CHD-)classification.[1,10] Although improvements in this respect have been made by the pediatric task force during the 5th World Symposium, the Nice classification would benefit from further improvements in acknowledging and providing a home for fetal/perinatal and developmental factors in pediatric PAH.

TOWARDS OPTIMAL TREATMENT STRATEGIES

PAH-targeted drugs in pediatric PAH

In pediatric PAH, treatment efficacy data and the development of evidence-based treatment guidelines are delayed due to a virtual absence of RCTs. Currently, only one of the PAH-targeted drugs is approved for children in Europe and none of these drugs is approved for children in the United States. We summarized the limited available data

on efficacy and safety of the PAH-targeted drugs in pediatric PAH in Chapter 4. Recently, both a consensus statement and guideline for the treatment of pediatric PAH have become available, which provide classes of recommendation and levels of evidence for the use of PAH-targeted drugs.[15,16] Although the PAH-targeted drugs received either class of recommendation I or IIa, level of evidence was either B or C indicating that data are limited or very limited. In contrast, in the latest adult guidelines the 'older' PAH-targeted drugs all have class of recommendation I with level of evidence A and the 'newer' ones have class of recommendation I with level of evidence B.[17] Without downgrading the importance of expertise of the treating physicians in pediatric PAH, this illustrates the high need for RCTs in pediatric PAH.

A major problem in the development of RCTs in pediatric PAH is the lack of a validated endpoint. Such an endpoint should be clinically meaningful, i.e. it should reflect how a patient feels, functions or survives.[18] Death may seem a robust endpoint, since improving prognosis is a main objective in (pediatric) PAH. However, using death as an endpoint requires long study durations and large study groups, which are both not feasible nor preferable in a rare and progressive disease as PAH.[19,20] Therefore, this would not be ethically justified precluding death as a useful endpoint in (pediatric) PAH. In adults, the six-minute walk distance (6MWD) has been used as primary endpoint in most pivotal RCTs.[21-23] In children with PAH, this is not a feasible endpoint since it cannot be reliably performed in infants and young children nor in children with physical and/or mental developmental delays. In the Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1) RCT, the percent change from baseline peak oxygen consumption measured during cardiopulmonary exercise testing (CPET) was used as primary endpoint.[24] However, CPET has the same limitations as the 6MWD regarding young age and developmental delays, but is also a more complex test for both the child and physician. In STARTS-1, CPET could only be performed in 115 out of 234 included children and was evaluable in only 106 children (45%).[24] This illustrates that CPET cannot be regarded a feasible endpoint in pediatric PAH.

Accelerometry, a non-invasive and relatively cheap tool, has been proposed as a potential endpoint in pediatric PAH.[20,25] In Chapter 8 we showed that accelerometry is feasible in children of various ages and that physical activity measured by accelerometry was markedly decreased in children with PAH compared to healthy, age- and sex-matched controls. As accelerometer output represents physical activity and thereby a direct reflection of how a patient functions, it can be regarded a clinically meaningful endpoint. Furthermore, accelerometer output correlated considerably with clinical disease severity markers and outcome.

Time to clinical worsening, which has been used as primary endpoint in more recent adult PAH RCTs[26,27], has also been proposed as study endpoint in pediatric PAH.[20,28] It is a composite endpoint that consists of several 'hard' and 'soft' components. Hard com-

ponents include death and lung transplantation, whereas soft components can include hospitalization, the need for therapy escalation or balloon atrial septostomy, progression of symptoms and functional deterioration defined by worsening 6MWD and/or World Health Organization functional class (WHO-FC). Recently, our group showed that the clinical worsening composite occurs early and frequently in the follow-up of children with PAH and that all components were highly predictive for death.[29] In clinical worsening, accelerometry may be of value as addition to or alternative for the 6MWD as soft component. This could make clinical worsening more applicable in children of all ages further strengthening its use as study endpoint in pediatric PAH.

Treatment strategies in pediatric PAH

For the oral and inhaled PAH-targeted drugs, based on pharmacokinetics and pharmacodynamics, rather strict dosing recommendations exist for their use in adults and children. In contrast, reported doses for subcutaneous and intravenous (IV/SC) prostanoids are less clear and vary significantly between studies.[5,30-32] Target doses as suggested in recent guidelines show a broad range, which may be insufficient to guide clinicians.[15,16] Furthermore, data regarding discontinuation of IV/SC prostanoids and transition to oral/inhaled therapies are very limited in pediatric PAH.[33,34] Given the unsatisfactory survival in pediatric PAH and in the search for optimal treatment strategies, data regarding the 'when, how and for how long' of IV/SC prostanoids would be very valuable. In Chapter 5, we provide a current clinical practice description regarding the use of IV/SC prostanoids in pediatric PAH, which were used in 36% of the children included in the original cohort as presented in Chapter 7. We show that approximately one-third of children is transitioned to oral/inhaled therapy and that successful transition with good longer-term outcome is predicted by near-normalization of pulmonary hemodynamics. In contrast, if there is no such normalization, even when the child is in WHO-FC I-II, transition to oral/inhaled therapy should not be considered. Furthermore, higher doses of IV/SC prostanoids may have beneficial effects on outcome, which appears to be independent from disease severity and time of IV/SC prostanoids initiation. As these data come from a retrospective cohort not specifically designed to evaluate the use of IV/SC prostanoids therapy, further studies specifically designed for this purpose are warranted.

Previously, treatment was often not escalated until a patient deteriorated. Due to evolving insights, a more aggressive goal-oriented treatment strategy is now being adopted in both adult and pediatric PAH.[35,36] This means that treatment is not only escalated when a patient deteriorates but also when a patients does not improve sufficiently, i.e. does not reach treatment goals within a period of therapy. Treatment goals, i.e. predefined improvements in clinical or hemodynamic parameters, are used to monitor clinical status and treatment efficacy in the individual patient and to guide treatment decisions.[11] Such parameter improvements could serve as treatment goals if they either

represent improved quality of life, e.g. improvement of exercise capacity, or a decrease in the chance of an outcome event, e.g. death or lung transplantation. In the latter case, the parameter has to meet the three criteria for surrogacy. First, the parameter should predict outcome. Secondly, it should be influenced by the given therapy, and thirdly such treatment-induced changes should reflect changes in outcome.[37,38] Thus, a parameter predicting outcome does not automatically qualify as parameter that could be used as treatment goal. In Chapters 6 and 7 we identified WHO-FC, plasma levels of (N-terminal pro) brain natriuretic peptide ([NTpro]BNP) and several hemodynamics obtained during cardiac catheterization (cardiac index, mean right atrial pressure, indexed pulmonary vascular resistance, mean pulmonary-to-systemic artery pressure ratio and acute vasodilator response) as disease characteristics significantly predicting outcome. Although these parameters may all be influenced by therapy, there is currently only limited evidence regarding treatment-induced changes in both adult and pediatric PAH. In children, treatment-induced changes in WHO-FC and plasma levels of NTproBNP (and also tricuspid annular plane systolic excursion) were recently shown to predict survival and improving these parameters thus qualifies as treatment goal in pediatric PAH.[38] Several echocardiographic parameters and cardiac magnetic resonance measurements have also been shown to predict outcome[39-43] but the current lack of data hampers their validation as treatment goals. A major advantage of accelerometry is that it provides a direct and objective measurement of how a patient functions, which could directly reflect quality of life. Improving accelerometer output, i.e. improving physical activity, therefore qualifies as valid treatment goal and could help guide treatment decisions in pediatric PAH.

In combination therapy with two or three PAH-targeted drugs, each targeting a different pathway, the drugs may have a synergistic effect on each other. Indeed, combination therapy, both upfront and add-on, has been shown to have beneficial effects on clinical status and outcome in adult PAH, which was recently confirmed in a systematic review and meta-analysis.[27,44-47] In children with PAH, data regarding combination therapy are scarce. Nevertheless, sildenafil add-on therapy was shown to have beneficial effects in children who deteriorate on bosentan therapy alone.[48] Furthermore, addition of inhaled or subcutaneous prostanoids to oral PAH-targeted therapy may be beneficial in a subset of children.[49,50] The data presented in Chapter 7 support the beneficial effects of combination therapy compared to monotherapy as children who received dual or triple PAH-targeted therapy during their disease course had favorable outcome compared to children who received only monotherapy, independent from disease severity.

Importantly, the value of non-drug treatments should not be forgotten in a time in which especially drug therapies receive so much attention. In fact, striving to optimal drug treatment strategies should not lead to too late non-drug treatments, such as balloon atrial septostomy, Potts shunt or lung transplantation. Especially the value of

the Potts shunt, i.e. a direct anastomosis between the left pulmonary artery and aorta, should be further established. In patients with suprasystemic pulmonary artery pressure, the Potts shunt leads to a direct pressure reduction of the right ventricle with systemic desaturation only in the lower parts of the body. To date, experiences seem favorable[51,52], but larger study groups may be required to reliably assess its value. As donor lungs remain scarce and will not come in time to save all children with end-stage PAH, the Potts shunt may serve as a bridge-to-transplantation or may even lead to deferring the need for lung transplantation in selected patients.[52]

Future studies should be directed towards providing efficacy and safety data for (combination) PAH-targeted therapy and the goal-oriented treatment strategy. Also, studies should be directed towards gathering further support for currently identified treatment goals and assessing the value of other parameters that may serve as treatment goals. Furthermore, the value of non-drug treatments, especially the Potts shunt, should be further evaluated.

TOWARDS OPTIMAL OUTCOME

There are quite large survival differences between different reporting centers/cohorts in pediatric PAH.[2,5,53-56] In Chapter 7 we showed that unadjusted survival rates differed between the three center cohorts. Importantly, these survival differences disappeared when correcting for disease severity. This confirms that reported survival rates cannot be simply compared to each other, since differences in inclusion criteria, selection of patients and the role of the referral center as regional or national referral center may lead to survival differences. Consequently, differences in reported survival rates do not simply reflect differences in quality of care or treatment strategies and should thus be interpreted with care. A careful and complete description of the studied cohort will help to identify potential differences between studies enhancing interpretation of (discrepancies in) reported survival rates.

Nowadays, reported 3- to 5-year transplantation-free survival rates of pediatric PAH range from approximately 60% to 85%[2,5,6,55-57], which is in line with the survival rates reported in this thesis. Although this indicates that survival of pediatric PAH has improved in recent years, it also shows that that 15% to 40% of children with PAH die or undergo lung transplantation within 3 to 5 years after diagnosis, which is obviously unsatisfactory and undesirable.

Optimal outcome, including both survival and quality of life, may be achieved by optimizing classification and treatment strategies in pediatric PAH. As none of the currently available PAH treatments can cure PAH, the development of new therapies is also of great interest. In pediatric PAH, gathering data for evaluating the value of classifications

or treatment strategies faces and will face several challenges inherent to the rareness and heterogeneity of pediatric PAH. One important challenge is how to obtain large enough study populations but there may be several solutions for this challenge. First, combining patient cohorts into multicenter or even multinational registries will increase study sizes. In recent years, such initiatives have led to valuable data in relatively large study groups and include the multinational Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry and the United States-based Registry to Evaluate Early and Long-Term Pulmonary Arterial Disease Management (REVEAL).[4,6] Furthermore, a collaboration between three major referral centers for pediatric PAH formed the basis for three Chapters of this thesis and resulted in one of the largest cohorts in pediatric PAH to date. It is important to keep in mind that in order to achieve comparability between patients from different centers, using strict and uniform inclusion criteria is essential in such collaborations. Secondly, as the care for pediatric PAH patients is centralized in many countries, including France, Spain, the United Kingdom and the Netherlands, there are national cohorts reporting on pediatric PAH.[2,3,53,56,57] Combining national cohorts may also lead to larger study groups. Combining (national) cohorts can also be used to find answers to specific questions. To illustrate this, bringing together all children with PAH after neonatal ASO for TGA from several (national) cohorts allowed for the first clinical characterization of this association contributing to clinical awareness of this severe complication after neonatal ASO for TGA. Multicenter and multinational collaborations and registries will lead to larger study groups and could provide valuable data on disease characteristics, treatment strategies, outcome and its predictors. But, such collaborations and registries also come with limitations. Incidence and prevalence rates of PAH cannot be determined. Also, treatment and follow-up strategies may differ between participating centers and cohorts hampering evaluation of treatment safety/efficacy and validation of candidate clinical endpoints and treatment goals. Such specific issues may be better evaluated in national or single-center cohorts in which standardized follow-up and treatment strategies are used and which allow for a more detailed collection of data, although study sizes will be smaller in such cohorts.

For determining efficacy of existing or newly developed PAH-targeted drugs or treatment strategies, RCTs are preferable. Next to the need of validated endpoints, that has been addressed previously, obtaining large enough study groups and allowing for relatively short study durations are important challenges. Furthermore, since almost all children with PAH receive off-label PAH-targeted therapy and the use of initial combination therapy is increasingly considered standard of care it would be ethically problematic to withdraw such therapies and trials must allow for the use of background (combination) therapy. These challenges may be overcome by so called smart-design trials.[58] Such trials do allow for multiple intervention stages, i.e. therapy escalations can be included and assessed also. For example, patients could start on monotherapy or combination

therapy and depending on the treatment response, i.e. whether treatment goals are reached or not, patients could either stay on their therapy or escalate quickly to dual or triple combination therapy. Consequently, drug efficacy, safety and pharmacokinetics and –dynamics could be assessed while securing individual needs.

In conclusion, although outcome of children with PAH has improved since the introduction of the PAH-targeted drugs, outcome in this vulnerable population remains unsatisfactory. This thesis increases the available amount of data and improves insights in classification, treatment and outcome in pediatric PAH. Furthermore, it presents a new candidate clinical endpoint for pediatric RCTs. Therefore, this thesis contributes to the development of optimal classification and treatment strategies, which will hopefully also lead to optimal outcome.

REFERENCES

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.
2. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: The UK pulmonary hypertension service for children 2001-2006. Heart. 2009;95(4):312-317.
3. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation. 2011;124(16):1755-1764.
4. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: A registry study. Lancet. 2012;379(9815):537-546.
5. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117-124.
6. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113-122.
7. van Albada ME, Berger RM. Pulmonary arterial hypertension in congenital cardiac disease--the need for refinement of the evian-venice classification. Cardiol Young. 2008;18(1):10-17.
8. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S43-54.
9. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: A comparison between clinical subgroups. Eur Heart J. 2014;35(11):716-724.
10. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI pediatric taskforce, panama 2011. Pulm Circ. 2011;1(2):286-298.
11. Berger RM. Pulmonary hypertension: Smaller kids, smaller steps. Lancet Respir Med. 2014;2(5):348-350.
12. Rudolph AM. Aortopulmonary transposition in the fetus: Speculation on pathophysiology and therapy. Pediatr Res. 2007;61(3):375-380.
13. Berman EB, Barst RJ. Eisenmenger's syndrome: Current management. Prog Cardiovasc Dis. 2002;45(2):129-138.
14. Hopper RK, Abman SH, Ivy DD. Persistent challenges in pediatric pulmonary hypertension. Chest. 2016;150(1):226-236.
15. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the american heart association and american thoracic society. Circulation. 2015;132(21):2037-2099.
16. Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. the european paediatric pulmonary vascular disease network, endorsed by ISHLT and DGPK. Heart. 2016;102 Suppl 2:ii67-ii85.
17. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS): Endorsed by: Association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.

18. Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. Clinical measurement in drug evaluation. New York: J. Wiley; 1995:3-22.
19. Gomberg-Maitland M, Bull TM, Saggar R, et al. New trial designs and potential therapies for pulmonary artery hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D82-91.
20. Adatia I, Haworth SG, Wegner M, et al. Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee. Pulm Circ. 2013;3(1):252-266.
21. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296-301.
22. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896-903.
23. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117(23):3010-3019.
24. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012;125(2):324-334.
25. European Medicines Agency: EMA/CHMP/213972/2010. Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500122492.pdf. Accessed June, 2016.
26. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809-818.
27. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373(9):834-844.
28. Haworth SG, Beghetti M. Assessment of endpoints in the pediatric population: Congenital heart disease and idiopathic pulmonary arterial hypertension. Curr Opin Pulm Med. 2010;16 Suppl 1:S35-41.
29. Ploegstra MJ, Arjaans S, Zijlstra WM, et al. Clinical worsening as composite study end point in pediatric pulmonary arterial hypertension. Chest. 2015;148(3):655-666.
30. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197-1208.
31. Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. Heart. 2007;93(6):739-743.
32. Siehr SL, Ivy DD, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: Long-term hemodynamics. J Heart Lung Transplant. 2013;32(5):546-552.
33. Ivy DD, Doran A, Claussen L, Bingaman D, Yetman A. Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. Am J Cardiol. 2004;93(7):943-946.
34. Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. Am J Cardiol. 2010;105(10):1485-1489.

35. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D60-72.
36. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117-26.
37. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med. 2012;31(25):2973-2984.
38. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J. 2014;44(6):1616-1626.
39. Moledina S, Pandya B, Bartsota M, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(3):407-414.
40. Ploegstra MJ, Roofthooft MT, Douwes JM, et al. Echocardiography in pediatric pulmonary arterial hypertension: Early study on assessing disease severity and predicting outcome. Circ Cardiovasc Imaging. 2014;8(1):10.1161/CIRCIMAGING.113.000878. Print 2015 Jan.
41. Takatsuki S, Nakayama T, Jone PN, et al. Tissue doppler imaging predicts adverse outcome in children with idiopathic pulmonary arterial hypertension. J Pediatr. 2012;161(6):1126-1131.
42. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol. 2010;106(3):430-436.
43. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J. 2013;165(6):1024-1031.
44. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013;369(4):330-340.
45. D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and eisenmenger physiology. Int J Cardiol. 2012;155(3):378-382.
46. Keogh A, Strange G, Kotlyar E, et al. Survival after the initiation of combination therapy in patients with pulmonary arterial hypertension: An australian collaborative report. Intern Med J. 2011;41(3):235-244.
47. Lajoie AC, Lauziere G, Lega JC, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: A meta-analysis. Lancet Respir Med. 2016;4(4):291-305.
48. Douwes JM, Roofthooft MT, Van Loon RL, et al. Sildenafil add-on therapy in paediatric pulmonary arterial hypertension, experiences of a national referral centre. Heart. 2014;100(3):224-230.
49. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr. 2011;158(4):584-588.
50. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. Am J Cardiol. 2012;110(11):1704-1709.
51. Baruteau AE, Serraf A, Levy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: Long-term results. Ann Thorac Surg. 2012;94(3):817-824.
52. Baruteau AE, Belli E, Boudjemline Y, et al. Palliative potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: Updated data from the first 24 patients. Eur J Cardiothorac Surg. 2015;47(3):e105-10.
53. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in france. Arch Cardiovasc Dis. 2010;103(2):66-74.

54. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660-665.
55. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106(9):1332-1338.
56. del Cerro Marin MJ, Sabate Rotes A, Rodriguez Ogando A, et al. Assessing pulmonary hypertensive vascular disease in childhood. data from the spanish registry. Am J Respir Crit Care Med. 2014;190(12):1421-1429.
57. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: A national cohort study. Heart. 2010;96(17):1401-1406.
58. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A "SMART" design for building individualized treatment sequences. Annu Rev Clin Psychol. 2012;8:21-48.

10

Summary (English and Dutch)

SUMMARY IN ENGLISH

Pulmonary arterial hypertension (PAH) is a rare, intrinsic and progressive disease of the small pulmonary arteries and has a poor prognosis. In recent years, the development of PAH-targeted drugs and the introduction of evidence-based treatment guidelines have greatly improved quality of life and survival in adult PAH patients. Due to important differences between adult and pediatric PAH, adult data cannot be simply extrapolated to children. Unfortunately, data in pediatric PAH remain scarce. In this thesis, we evaluated classification, treatment strategies and (predictors of) survival in pediatric PAH. Furthermore, we assessed the value of a potential clinical endpoint for pediatric randomized controlled trials. **Chapter 1** provides a comprehensive background of PAH and describes the aims and outline of this thesis.

Chapter 2 focuses on children with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). CHD is a frequent cause of pediatric PAH with diverse etiology and outcome. In adults, the value of the proposed shunt-based Nice congenital heart disease classification (Nice-CHD-classification, Nice, France, 2013) regarding differences in disease severity and outcome between groups was recently reported. Data in children were lacking. We aimed to describe phenotypic heterogeneity in pediatric PAH-CHD, to assess the value of the Nice-CHD-classification and to evaluate whether this classification reflects patient and disease characteristics and survival. We selected all children with CHD from the cohort described in Chapter 7, described anatomy, physiology and repair status of the CHD and classified all children according to the Nice-CHD-classification. In total, 134 children with PAH and CHD were included. Most children (77%) had simple pre- or post-tricuspid shunt-defects and 11% had complex shunt-defects. Eleven percent could not be classified in the Nice-CHD-classification. Regarding the Nice-CHD-classification, 32 children were classified as having Eisenmenger syndrome, 19 as having PAH associated with left-to-right shunts, 26 as having PAH with coincidental CHD, and 40 as having post-operative PAH-CHD. We identified clinically relevant differences in patient and disease characteristics between groups especially regarding comorbidities, types of CHD, hemodynamic profile and treatment intensity. In exploratory analyses, we did not observe differences in transplantation-free survival between groups. We conclude that the recently proposed Nice-CHD-classification supports clinical characterization of children with PAH-CHD but that further refinement is needed in order to adequately classify all children with PAH-CHD.

Chapter 3 focuses on the concurrence of PAH after neonatal arterial switch operation (ASO) for transposition of the great arteries (TGA). Although the development of PAH after successful and timely ASO for TGA is not to be expected, it is a clinically recognized entity in pediatric pulmonary hypertension (PH) centers. We aimed to clinically characterize this entity by presenting an international cohort of children with PAH after

neonatal ASO for TGA and describing its epidemiology and clinical course. We identified 25 children from nine dedicated pediatric PH centers in Europa and the United States, including four national registries (United Kingdom, France, Spain and the Netherlands). Children with residual hemodynamically relevant shunt-defects, pulmonary branch stenosis or impaired left ventricular function were not included. No other causes for or associated conditions with PAH were identified in any of the children. Most children (84%) underwent a Rashkind procedure within the first days after birth and median age at ASO was 8 days. Two phenotypes could be distinguished in this cohort: early-onset PAH, presenting weeks to months after ASO, and late-onset PAH, presenting years after ASO. Patient and disease characteristics did not differ between these two groups. Despite the intense use of PAH-targeted therapies, Potts shunt- and transplantation-free survival was poor with a 5-year survival rate of 73% after ASO and 58% after first PAH detection. Based on the literature, we estimated the incidence of PAH after neonatal ASO for TGA to be 0.6 to 1.0%. We speculate on the underlying role of altered prenatal pulmonary hemodynamics and of genetic susceptibility in these children. Also, we advocate that the lifelong follow-up of children who undergo neonatal ASO for TGA should include screening for PAH.

Chapter 4 provides an overview of the currently available drug and non-drug treatments for PAH and summarizes the limited available pediatric safety and efficacy data for these treatments. Furthermore, it focuses on the use of combination therapy and the goal-oriented treatment strategy including currently used treatment goals.

Chapter 5 focuses on children who were treated with intravenous or subcutaneous (IV/SC) prostanoids. We provide a current clinical practice description of the use of IV/SC prostanoids, including time of initiation, dosing and transition to oral/inhaled therapies. We selected all children who were treated with IV/SC prostanoids from the cohort described in Chapter 7. In total, 98 of the 275 children of the original cohort (36%) were selected. Most children had severe PAH at time of IV/SC prostanoids initiation and in most children IV/SC prostanoids were initiated within one year after diagnosis. The median calculated dose during the therapy period was 37 ng/kg/min, ranged from 4 to 136 ng/kg/min, was highest in the New York cohort and lowest in the Dutch cohort. During their disease course, IV/SC prostanoids were discontinued in 29 children and all were switched to oral/inhaled therapies. At time of discontinuation 12 children had near-normalization of pulmonary hemodynamics and all these children had an uneventful follow-up. In the remaining 17 children, there was no near-normalization of pulmonary hemodynamics. In this group IV/SC prostanoids had to be restarted in 4 children, 2 children died and 1 child underwent lung transplantation. In the 64 children in whom IV/SC prostanoids were continued, a higher calculated dose was associated with better transplantation-free survival. We conclude that near-normalization of pulmonary hemodynamics while on IV/SC prostanoids therapy predicted a successful transition to oral/

inhaled therapy in pediatric PAH. If there is no near-normalization, transition should not be considered. Furthermore, higher doses of IV/SC prostanoids may have a beneficial effect on outcome.

Chapter 6 provides a systematic review and meta-analysis on prognostic factors in pediatric PAH. We searched Medline, EMBASE and Cochrane Library on April 1st 2014 to identify studies that described predictors of mortality or lung transplantation exclusively in pediatric PAH. Of 1053 identified citations, 25 were included for further analysis. World Health Organization functional class (WHO-FC), (N-terminal pro) brain natriuretic peptide, mean right atrial pressure, indexed pulmonary vascular resistance, cardiac index and acute vasodilator response were identified as consistently reported prognostic factors in pediatric PAH. We conclude that these parameters are useful clinical tools to assess prognosis and therefore should be incorporated in treatment strategies and guidelines for children with PAH. It should be noted that this review does not preclude the potential of other reported candidate prognostic factors, including parameters derived by echocardiography and cardiac magnetic resonance imaging, but rather identifies directions for further research to address gaps in current evidence.

In **Chapter 7** we describe patient, disease and treatment characteristics and outcome of a consecutive contemporary cohort of children with PAH seen in the Children's Hospital Colorado in Aurora, the Columbia University Medical Center, New York (NY) and the Dutch National Network for Pediatric PH at the University Medical Center Groningen/ Beatrix Children's Hospital, the Netherlands. All pediatric PAH patients who visited these centers between 2000 and 2010 and who had the diagnosis of PAH confirmed during cardiac catheterization after 1997 were included. In total, 275 children were included: 135 from NY, 93 from Denver and 47 from the Netherlands. Children in the Dutch cohort had worse disease at time of diagnosis than children in the Denver and NY cohorts: higher WHO-FC, shorter six-minute walk distance and worse hemodynamics. Overall 1-, 3-, 5- and 7-year transplantation-free survival rates were 96%, 91%, 89% and 79%, respectively. Unadjusted survival of children in the NY cohort was more favorable than survival of children in the other two cohorts. We identified diagnosis, WHO-FC, indexed pulmonary vascular resistance and mean pulmonary-to-systemic artery pressure ratio to be independent predictors of outcome that could explain the observed survival differences among the center cohorts. Moreover, treatment with PAH-targeted combination therapy during the study period was independently associated with favorable outcome.

In **Chapter 8** we evaluate a candidate clinical endpoint in pediatric PAH, namely physical activity (PA) as measured by accelerometry. In pediatric PAH, evidence-based treatment guidelines are currently lacking and its development is hampered by a virtual lack of randomized controlled trials (RCTs). A major problem in trial design is the lack of a feasible clinical endpoint in this population. We evaluated the value of accelerometry in pediatric PAH by comparing PA measured by accelerometry in children with PAH to that

in healthy controls and assessing whether accelerometer output correlates with disease severity and outcome in pediatric PAH. We included children who visited the outpatient clinic of the Dutch National Referral Center for PH in Childhood between June 2013 and March 2016. Controls were recruited from children who visited the outpatient cardiology clinic of the Beatrix Children's Hospital, University Medical Center Groningen for screening for cardiac disease but appeared to have no, or not hemodynamically relevant, cardiac disease. Children were instructed to wear the accelerometer for 7 consecutive days. Vector magnitude counts per minute (VM CPM) and PA intensity levels (classified as sedentary, light, moderate and vigorous PA) were defined as accelerometer outcomes. In total, 29 children with PAH and 60 age- and sex-matched controls wore the accelerometer. There was good accelerometer wear compliance, both in children with PAH and in controls. PA in children with PAH was markedly decreased compared to controls, especially moderate and vigorous PA. Accelerometer outcomes correlated considerably with clinical disease severity markers, i.e. six-minute walk distance and WHO-FC, and may also predict outcome. We conclude that PA can be objectively assessed in children of various ages using accelerometry and that accelerometry provides an objective and direct measurement of how a patients functions. Therefore, accelerometer output qualifies as clinically meaningful endpoint for clinical trials in pediatric PAH, although its use needs to be validated in a second, larger population.

Chapter 9 provides a general discussion of the results of this thesis including directions for future research.

NEDERLANDSE SAMENVATTING

Pulmonale arteriële hypertensie (PAH) is een zeldzame, intrinsieke en progressieve ziekte van de kleine longvaten en heeft een slechte prognose. De ontwikkeling van PAH-gerichte medicatie en de ontwikkeling van evidence-based richtlijnen voor diagnostiek en behandeling van PAH heeft de afgelopen jaren geleid tot een sterke verbetering van de kwaliteit van leven en overleving van volwassenen met PAH. Vanwege belangrijke verschillen tussen PAH in volwassenen en PAH in kinderen, kunnen data verkregen in volwassenen niet zomaar geëxtrapoleerd worden naar kinderen. Data in de pediatrische PAH-populatie zijn tot op de dag van vandaag schaars. In dit proefschrift evalueren we classificatie, behandelstrategieën in het huidige tijdperk van PAH-gerichte medicatie en (voorspellers voor) de overleving van kinderen met PAH. Daarnaast evalueren we de waarde van een potentieel eindpunt dat gebruikt zou kunnen worden in gerandomiseerde klinische trials in kinderen met PAH. In **Hoofdstuk 1** geven we een bondige introductie van PAH in kinderen en beschrijven we de doelstellingen en inhoud van dit proefschrift.

In **Hoofdstuk 2** focussen we ons op kinderen met PAH geassocieerd met een aangeboren hartafwijking (PAH-CHD). Aangeboren hartafwijkingen vormen een belangrijke oorzaak van PAH, waarbij verschillende afwijkingen leiden tot verschillen in ziektepresentatie, -verloop en -uitkomst. Recent is gebleken dat de voorgestelde classificatie voor PAH-CHD (Nice-CHD-classificatie), die gebaseerd is op het shunt-defect, in volwassenen met PAH inderdaad groepen onderscheid met verschillende patiënt- en ziektekarakteristieken en een verschillende uitkomst. De mogelijke waarde van deze classificatie in kinderen was nog niet geëvalueerd. In dit hoofdstuk beschrijven we de fenotypische heterogeniteit in kinderen met PAH-CHD en evalueren we de waarde van de Nice-CHD-classificatie in kinderen met PAH. Voor deze studie hebben we alle kinderen met een aangeboren hartafwijking geselecteerd uit het cohort beschreven in Hoofdstuk 7. We hebben de anatomie, fysiologie en of de afwijkingen gecorrigeerd zijn of niet beschreven en vervolgens de kinderen ingedeeld volgens de Nice-CHD-classificatie. In totaal zijn er 134 kinderen met PAH en een aangeboren hartafwijking geïdentificeerd. Van deze kinderen had 77% een simpel shunt-defect en 11% had een complex shunt-defect. Elf procent van de kinderen hadden diverse andere hartafwijkingen en konden niet geclassificeerd worden volgens de Nice-CHD-classificatie. Er waren 32 kinderen met het Eisenmenger syndroom, 19 kinderen met PAH geassocieerd met een links-rechts shunt, 26 kinderen met PAH en een aangeboren hartafwijking niet verklarend voor de PAH en 40 kinderen met post-operatieve PAH. Er waren klinisch relevante verschillen in patiënt- en ziektekarakteristieken tussen deze vier groepen, met name in comorbiditeit, type aangeboren hartafwijking, hemodynamiek en therapie intensiteit. In een exploratieve analyse zagen we geen verschillen in overleving vrij van longtransplantatie tussen de

groepen. We concluderen dat de Nice-CHD-classificatie bijdraagt aan klinische classificatie van kinderen met PAH-CHD, maar dat verdere verbetering nodig is om alle kinderen met dit ziektebeeld op een juiste manier te kunnen classificeren.

In **Hoofdstuk 3** focussen we ons op de associatie tussen één specifieke aangeboren hartafwijking en PAH, namelijk de transpositie van de grote vaten (TGA) neonataal gecorrigeerd met een arteriële switchoperatie (ASO). Hoewel PAH na een succesvolle ASO niet te verwachten is, blijkt dit toch een klinisch herkende associatie te zijn in centra voor pulmonale hypertensie in kinderen. We geven een klinische beschrijving van dit ziektebeeld in een internationaal cohort van kinderen met PAH na een neonatale ASO voor TGA en beschrijven de epidemiologie en het ziektebeloop. In totaal hebben we 25 kinderen met dit ziektebeeld geïdentificeerd uit negen centra voor pulmonale hypertensie op de kinderleeftijd, waarvan vier nationale cohorten (Engeland, Frankrijk, Spanje en Nederland). Kinderen met een hemodynamische belangrijke rest shunt, pulmonaal tak stenose of verminderde linker ventrikelfunctie werden niet geïncludeerd in deze studie. Het merendeel van de kinderen (84%) onderging een Rashkind-procedure in de eerste levensdagen en de ASO werd op een mediane leeftijd van 8 dagen uitgevoerd. We konden twee fenotypes onderscheiden: PAH die weken tot maanden na de ASO werd gedetecteerd en PAH die pas na jaren gedetecteerd werd. Er waren geen verschillen in patiënt- en ziektekarakteristieken tussen deze twee groepen. Ondanks intensief gebruik van PAH-gerichte medicatie was de prognose in dit cohort slecht: de 5-jaars overleving vrij van Potts shunt en longtransplantatie was 73% na ASO en 58% na PAH detectie. Gebaseerd op de literatuur schatten we de incidentie van PAH na neonatale ASO voor TGA op 0.6 tot 1.0%. We speculeren dat prenatale pulmonale hemodynamiek en onderliggende genetische defecten een rol kunnen spelen bij het ontstaan van deze associatie. Daarnaast pleiten we ervoor dat kinderen die een neonatale ASO voor TGA hebben ondergaan tijdens de levenslange controles ook gescreend worden op PAH.

In **Hoofdstuk 4** geven we een overzicht van de op dit moment beschikbare therapieën voor PAH, waarbij we ons zowel richten op medicatie als op interventies. We geven een overzicht van de beperkte hoeveelheid pediatrische data wat betreft veiligheid en effectiviteit. Daarna focussen we ons op combinatie therapie, de zogenaamde doelgeoriënteerde behandelingsstrategie en momenteel gebruikte behandeldoelen.

In **Hoofdstuk 5** richten we ons op kinderen met PAH die behandeld worden met intraveneuze of subcutane (IV/SC) prostanoïden. We geven een overzicht van hoe kinderen met deze middelen behandeld worden in het huidige tijdperk van PAH-gerichte medicatie, inclusief timing van start, dosering en switch naar inhalatie/orale middelen. Voor deze studie hebben we alle kinderen met PAH die behandeld zijn met deze middelen geselecteerd uit het cohort beschreven in Hoofdstuk 7. In totaal ontvingen 98 van de 275 kinderen uit het originele cohort (36%) IV/SC prostanoïden. De meeste kinderen hadden ernstige PAH op het moment van start en bij de meeste kinderen werden IV/SC

prostanoïden gestart binnen 1 jaar na diagnose. De mediane berekende dosis was 37 ng/kg/min en wisselde van 4 tot 136 ng/kg/min. Deze dosis was het hoogst in kinderen uit New York en het laagst in kinderen uit Nederland. In 29 kinderen werd de behandeling gestopt en in al deze kinderen werd geswitcht naar inhalatie/orale PAH-medicatie. Twaalf van deze kinderen hadden (bijna) normalisatie van de pulmonale hemodynamiek ten tijde van de switch en al deze kinderen hadden een event-vrije follow-up. Van de 17 kinderen zonder (bijna) normalisatie werden IV/SC prostanoïden herstart in 4 kinderen, overleden er 2 en onderging 1 kind een longtransplantatie. In de 64 kinderen die niet stopten met IV/SC prostanoïden was een hogere berekende dosis geassocieerd met een beter overleving. We concluderen dat (bijna) normalisatie van de pulmonale hemodynamiek een succesvolle switch van IV/SC prostanoïden naar orale/inhalatie medicatie voorspelt en dat deze switch niet overwogen moet worden in kinderen zonder (bijna) normalisatie. Daarnaast concluderen we dat een hogere dosis IV/SC prostanoïden mogelijk een gunstig effect heeft op de overleving van kinderen met PAH.

Hoofdstuk 6 bestaat uit een systematische review en meta-analyse over voorspellers voor overleving in kinderen met PAH. We doorzochten Medline, EMBASE en de Cochrane Library op 1 april 2014 en identificeerden studies die voorspellers voor dood of longtransplantatie beschreven in kinderen met PAH. Uiteindelijk includeerden we 25 van de 1053 geïdentificeerde citaties voor verdere analyse. Zes variabelen werden consistent gerapporteerd als voorspellers in kinderen met PAH: WHO functionele klasse (WHO-FC), (N-terminal pro) brain natriuretisch peptide, gemiddelde rechter atriumdruk, geïndexeerde pulmonale vaatweerstand, cardiale index en acute vasodilatator respons. We concluderen dat deze parameters in de klinische praktijk gebruikt kunnen worden om de prognose te bepalen en dat deze parameters daarom deel moeten uitmaken van behandelstrategieën en richtlijnen voor kinderen met PAH. Daarnaast is het belangrijk om te noemen dat we met deze review de mogelijke waarde van andere potentiële voorspellers, waaronder echocardiographie en cardiale MRI, niet willen uitsluiten, maar willen laten zien dat hiernaar meer onderzoek nodig is.

In **Hoofdstuk 7** beschrijven we een hedendaags cohort van kinderen met PAH die tussen 2000 en 2010 gezien zijn in drie grote verwijscentra voor PAH op de kinderleeftijd: het Kinderziekenhuis Colorado in Aurora, het Columbia Universitair Medisch Centrum in New York, en het Nederlandse Landelijk Netwerk voor Pulmonale Hypertensie op de Kinderleeftijd, Beatrix Kinderziekenhuis/Universitair Medisch Centrum Groningen. Alle kinderen die na 1997 gediagnosticeerd zijn met een hartkatheterisatie werden geïncludeerd in dit cohort. In totaal includeerden we 275 kinderen: 135 uit New York, 93 uit Denver en 47 uit Nederland. Kinderen uit het Nederlandse cohort waren zieker op het moment van diagnose dan kinderen uit de Denver en New York cohorten: hogere WHO-FC, lagere 6-minuten loopafstand en slechtere hemodynamiek. Overleving vrij van longtransplantatie was respectievelijk 96%, 91%, 89% en 79% op 1, 3, 5 en 7

jaar na diagnose. Kinderen in het New York cohort hadden een betere overleving dan kinderen in de andere twee cohorten. Diagnose, WHO-FC, geïndexeerde pulmonale vaatweerstand en gemiddelde pulmonale-tot-systemische arteriële druk ratio bleken onafhankelijke voorspellers voor overleving, die de verschillen in overleving tussen de cohorten konden verklaren. Daarnaast was behandeling met PAH-gerichte combinatie therapie onafhankelijk geassocieerd met een betere overleving.

In **Hoofdstuk 8** evalueren we lichamelijke activiteit gemeten met accelerometrie als potentieel klinisch eindpunt in kinderen met PAH. Momenteel zijn er geen evidence-based behandelrichtlijnen voor kinderen met PAH en de ontwikkeling hiervan wordt belemmerd door het nagenoeg afwezig zijn van gerandomiseerde klinische trials. Het opzetten van zulke klinische trials wordt bemoeilijkt doordat er geen bruikbaar klinisch eindpunt is voor deze populatie. We evalueren de waarde van accelerometrie bij kinderen met PAH door de mate van lichamelijke activiteit van deze kinderen te vergelijken met gezonde controles die gematched zijn op leeftijd en geslacht, en door te bekijken of de mate van lichamelijke activiteit van kinderen met PAH correleert met parameters voor ziekte ernst en uitkomst. Kinderen met PAH die de polikliniek van het Nationale Expertisecentrum voor Pulmonale Hypertensie op de Kinderleeftijd (Beatrix Kinderziekenhuis, Universitair Medisch Centrum Groningen) bezochten tussen juni 2013 en maart 2016 werden geïncludeerd in deze studie. Kinderen die de polikliniek kindercardiologie van het Beatrix Kinderziekenhuis bezochten voor screening op hartziekten en deze niet bleken te hebben (in ieder geval geen hemodynamisch belangrijke hartziekten) werden gevraagd als controles. Alle kinderen werden geïnstrueerd de accelerometer gedurende 7 dagen te dragen. Vector magnitude counts per minuut (VM CPM) en intensiteit van de lichamelijke activiteit, gedefinieerd als rust, lichte, matige en zware activiteit, werden gedefinieerd als accelerometer uitkomstmaten. In totaal droegen 29 kinderen met PAH en 60 leeftijd- en geslachtgematchte controles de accelerometer, met een goede studie compliantie. Kinderen met PAH waren minder actief dan de controle kinderen. Zij spendeerden met name minder tijd in matige en zware activiteiten. De accelerometer uitkomstmaten correleerden significant met klinische parameters voor ziekte ernst (WHO-FC en zes-minuten loopafstand) en zijn mogelijke ook voorspellend voor uitkomst. Daarom concluderen we dat accelerometrie gebruikt kan worden als klinisch betekenisvol eindpunt voor klinische trials in pediatrische PAH, wel met de kanttekening dat het gebruik van accelerometers verder gevalideerd dient te worden in een tweede, grotere populatie.

Hoofdstuk 9 bestaat uit een algemene discussie van de resultaten van dit proefschrift en biedt suggesties voor toekomstig onderzoek.

Epilogue

BIBLIOGRAPHY

Publications

Zijlstra WM, Douwes JM, Rosenzweig EB, Schokker S, Krishnan U, Roofthooft MT, Miller-Reed K, Hillege HL, Ivy DD, Berger RM. Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies.
J Am Coll Cardiol 2014;63(20):2159-2169.

Ploegstra MJ, Douwes JM, Roofthooft MT, **Zijlstra WM**, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension.
Eur Respir J 2014;44(6):1616-1626.

Zijlstra WM, Ploegstra MJ, Berger RM. Current and advancing treatments for pulmonary arterial hypertension in childhood.
Expert Rev Respir Med. 2014 Oct;8(5):615-628.

Ploegstra MJ, **Zijlstra WM**, Douwes JM, Hillege HL, Berger RM. Prognostic factors in pediatric pulmonary arterial hypertension: A systematic review and meta-analysis.
Int J Cardiol 2015;184:198-207.

Ploegstra MJ, Arjaans S, **Zijlstra WM**, Douwes JM, Vissia-Kazemier TR, Roofthooft MT, Hillege HL, Berger RM. Clinical Worsening as Composite Study End Point in Pediatric Pulmonary Arterial Hypertension.
Chest 2015;148(3):655-666.

Zijlstra WM, Douwes JM, Ploegstra MJ, Krishnan U, Roofthooft MT, Hillege HL, Ivy DD, Rosenzweig EB, Berger RM. Clinical classification in pediatric pulmonary arterial hypertension associated with congenital heart disease.
Pulm Circ 2016;6(3):302-312.

Zijlstra WM, Elmasry O, Pepplinkhuizen S, Ivy DD, Bonnet D, Luijendijk P, Lévy M, Gavilan JL, Torrent-Vernetta A, Mendoza A, del Cerro MJ, Moledina S, Berger RM. Pulmonary arterial hypertension in children after neonatal arterial switch operation.
Accepeted for publication in Heart.

Oral presentations

Zijlstra WM, Elmasry O, Pepplinkhuizen S, Ivy DD, Bonnet D, Luijendijk P, Lévy M, Gavilan JL, Torrent A, Mendoza A, Jesus del Cerro M, Moledina S, Berger RM. Pulmonary arterial hypertension in children with transposition of the great arteries after successful neonatal arterial switch operation. Annual meeting of the AEPC, Rome, Italy, June 2016.

Poster presentations

Zijlstra WM, Douwes JM, Rosenzweig E, Schokker S, Krishnan U, Miller-Reed K, Hillege HL, Ivy DD, Berger RM. Transatlantic survival differences in pediatric pulmonary hypertension: clues to a better understanding of disease characteristics and treatment. Annual meeting of the ATS, Philadelphia, Pennsylvania, United States, May 2013.

Zijlstra WM, Douwes JM, Rosenzweig E, Schokker S, Krishnan U, Miller-Reed K, Hillege HL, Ivy DD, Berger RM. Children with pulmonary arterial hypertension (PAH) associated with congenital heart disease are treated less intensively with PAH-targeted drugs compared to children with idiopathic/hereditary PAH. Annual meeting of the ESC, Amsterdam, the Netherlands, August 2013.

Zijlstra WM, Douwes JM, Rosenzweig EB, Schokker S, Krishnan U, Roofthooft MT, Miller-Reed K, Hillege JL, Ivy DD, Berger RM. PAH-targeted combination therapy may be associated with improved outcome in pediatric PAH patients. 1st Conference on Pediatric and Neonatal Pulmonary Vascular Disease, Groningen, the Netherlands, October 2013.
Prize for best poster presentation.

Ploegstra MJ, **Zijlstra WM**, Douwes JM, Hillege HL, Berger RM. Prognostic Factors in Pediatric Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis. Annual meeting of the ATS, Denver, Colorado, United States, May 2015.

Zijlstra WM, Douwes JM, Ploegstra MJ, Krishnan U, Roofthooft MT, Hillege JL, Ivy DD, Rosenzweig EB, Berger RM. Clinical Classification in Pediatric Pulmonary Arterial Hypertension Associated with Congenital Heart Disease. Annual meeting of the ATS, Denver, Colorado, United States, May 2015.

Zijlstra WM, Elmasry O, Pepplinkhuizen S, Ivy DD, Bonnet D, Luijendijk P, Lévy M, Gavilan JL, Torrent A, Mendoza A, Jesus del Cerro M, Moledina S, Berger RM. Pulmonary arterial hypertension in children with transposition of the great arteries after successful neonatal arterial switch operation. 2nd Conference on Pediatric and Neonatal Pulmonary Vascular Disease, Groningen, the Netherlands, October 2015.

ABOUT THE AUTHOR

Willemijn Marie Hélène Zijlstra was born in Groningen on the 25th of June 1989. In 2007, she finished high school at the Drachtster Lyceum, Drachten and moved back to Groningen to study Medicine at the University of Groningen. After completing her bachelor degree, she became president of the International Student Congress on (bio)Medical Sciences 2011. At that time Willemijn also initiated her research at the department of Pediatric Cardiology of the Beatrix Children's Hospital/University Medical Center Groningen under the guidance of professor R.M.F. Berger, focusing on pediatric pulmonary arterial hypertension. This resulted in a MD/PhD-traject honored by the Junior Scientific Masterclass. During the following years Willemijn did her internships and worked on her research project. For this project she also worked at the Children's Hospital Colorado, Denver, Colorado, United States, under the guidance of her second promotor professor D.D. Ivy. Furthermore, she served as a tutor and exam trainer for bachelor students. In 2016 Willemijn both graduated from medical school and finished her PhD-thesis which she hopes to defend on the 15th of February 2017. Willemijn now lives in Amsterdam and works at the Cardiology department of the Noordwest Ziekenhuisgroep, Alkmaar.

DANKWOORD

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