Shaping the future of paediatric pulmonary arterial hypertension
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General discussion

Pulmonary arterial hypertension (PAH) is a detrimental disease for which there is no cure. Despite our best efforts to slow disease progression using PAH targeted therapies, PAH leads to death, the necessity of (heart-)lung transplantation or palliative surgery (Potts shunt or atrial septostomy) in many children that have the disease. The introduction of PAH targeted therapies has led to an improvement of survival rates in paediatric PAH. However, despite this improvement these survival rates are still very much unfavourable (Chapter 2). This leads to the conclusion that we need to strive to a further improvement of the clinical care for children with PAH. However, in order to do so, we need paediatric data to understand the disease and provide the necessary evidence upon which we can base our treatment strategies. This data has been lacking. The studies described in this thesis have provided essential data on the epidemiology, determinants of outcome and treatment strategies of paediatric PAH, that contribute to resolving the current unmet needs in paediatric PAH and will help shape the future of paediatric pulmonary arterial hypertension treatment.

Epidemiology

Due to its progressive nature, early diagnosis and treatment initiation is vital in PAH in order to achieve a favourable prognosis. It has been recognized that there is often a substantial delay in diagnosis for paediatric PAH. This delay can be attributed to a presentation with non-specific symptoms, variation in clinical presentation and disease course, and the rareness of pulmonary hypertension that impedes paediatricians from gaining sufficient experience with the disease.

In order to build up enough experience with the rare disease of PAH it is advised to centralize care for paediatric PAH. In the Netherlands this centralization has taken shape in the Dutch National Network for Paediatric Pulmonary Hypertension. Within this network the diagnosis and treatment initiation are performed in one national expert centre. The care for these patients is shared with nine network centres, based on a national consensus guideline on the diagnosis, treatment and follow-up. The referral of all Dutch paediatric PAH patients to a national expert centre ensures sufficient patient numbers to gain specialised knowledge on PAH and allows the development of an infrastructure that is necessary to manage the disease. The shared care for these patients with the nine network centres, the largest paediatric cardiology care centres of the Netherlands, allows for the build-up of clinical experience with the disease warranting early disease detection within these centres. In order to further optimize pulmonary hypertension awareness, the Dutch National Network for Paediatric Pulmonary Hypertension has initiated a national pulmonary hypertension awareness program. This program includes the publication of the national standard for the diagnosis and treatment of pulmonary hypertension, which is regularly send to all Dutch paediatricians and paediatric residents and is repeatedly distributed during national paediatric conferences. National network meetings are organized twice yearly with the goal to share knowledge and discuss interesting case histories. Furthermore, the European Conference on Neonatal and
Paediatric Pulmonary Vascular Disease is organized in The Netherlands every two years. At this international conference the most recent scientific knowledge is shared by international experts on paediatric PAH, allowing the Dutch paediatricians to gain this knowledge in a close to home setting.

Centralization of care such as in the Dutch national network gave opportunities to study large cohorts of children with PAH. In the past decades this has led to several reports on the epidemiology and clinical characterization of paediatric PAH. This data enabled us to provide reliable incidence and prevalence numbers and give a summarizing overview of the epidemiology and clinical presentation of the disease (chapter 2), which will help to recognize and identify the disease in an earlier state, allowing for more early treatment initiation.

Emerging data on risk factors for the development of PAH, associated diseases and syndromes, hereditary occurrence, and the discovery of associated germline mutations is especially of interest. This data gives the opportunity to detect specific conditions associated with PAH in order to provide the treatment specifically effective for the disease, as illustrated by the clinical observation of pulmonary hypertension associated with renal thrombotic microangiopathy in cobalamin C deficiency. Furthermore it enables screening of children with high risk of developing PAH due to associated conditions, family members with PAH or associated germline mutations. Screening for PAH may in future help to discover the disease in the earliest and maybe even subclinical phase, allowing for early treatment initiation.

**Determinants of outcome**

After diagnosis, treatment of paediatric PAH is adapted to the severity of the patient’s disease. Patients with more severe disease or more rapid disease progression need to be treated more intensively. During the course of treatment there is a stepwise approach in which therapy is intensified by adding medications to achieve combination therapy, either when a patients clinical condition deteriorates or does not improve despite the initiated therapy. In order to evaluate a patients disease severity and monitor clinical improvement or deterioration during their treatment we need determinants of outcome that can be measured repeatedly during follow-up to monitor disease progression. However data on determinants of outcome in paediatric PAH had been lacking. Below the determinants of outcome identified in this thesis will be discussed.

The first step in the currently accepted treatment algorithm comprises of determining acute vasodilator response during right heart catheterization. Acute vasodilator response has been shown to identify adult idiopathic/heritable PAH (IPAH/HPAH) patients that have improved outcome and show a sustained response to calcium channel blocker (CCB) therapy. For children with PAH, the prevalence and prognostic ability of acute vasodilator response had been unclear due to a lack of data.

Although it was long thought that children with PAH have a more vasoreactive vascular bed compared to adult PAH patients, we could demonstrate in Chapter 3 and 4 that
the prevalence of acute vasodilator response in children with IPAH/HPAH is comparable to adult patients. Previous studies showed a high percentage of responders in paediatric PAH, ranging 35%-56% compared to 5-17% in adult IPAH patients. However, the use of specific paediatric response criteria in paediatric studies (the Barst criteria that in time evolved to the REVEAL paediatric criteria and differed from the criteria used in adult PAH), hampered direct comparisons between the observed percentages. Our studies, described in chapter 3 and 4 showed that 8-15% of paediatric IPAH/HPAH patients were acute responder according to the Sitbon criteria, which is a percentage that is similar to the percentage of Sitbon responders reported in adult patients. In chapter 4 we were able to show that the Sitbon criteria for acute vasodilator response, that are more strict than the paediatric criteria, indeed identified acute responders more selectively. This explains why the percentage of responders reported in adult patients using the Sitbon criteria was lower than the percentage of responders reported in children using the less strict paediatric criteria. So in conclusion the occurrence of acute vasodilator response in paediatric IPAH/HPAH equals the occurrence in adult IPAH/HPAH and the reported difference in the occurrence of acute vasodilator response between children and adults can be attributed to the use of different response criteria.

The fact that it was long thought that children with IPAH are more vasoreactive than adult IPAH patients is a good example of how the use of different definitions, in this case of acute vasodilator response, can lead to misinterpretation of reported data. As we have outlined in chapter 3a, it is of utmost importance to clearly describe the definitions used when reporting study data and to state where these definitions may deviate from previous reported data, in order to prevent such misunderstandings.

Children with IPAH/HPAH that are classified as acute responders have better outcome compared to nonresponders. However, as one might expect, the criteria used to identify responders matter. A subsequent study in a worldwide cohort of children with PAH, described in chapter 4, revealed that the more strict Sitbon criteria were superior in identifying patients with improved outcome. Furthermore, patients identified as responders according to the REVEAL-paediatric criteria but not according to the Sitbon criteria, appeared to have a worse outcome, comparable to nonresponders. However, a personal evaluation of acute vasodilator response by the treating physician proved to identify patients with improved outcome even better. The responders identified by the treating physicians had a more favourable hemodynamic profile, which may have been taken into account during the process of identifying them to be a responder. Therefore, even though the Sitbon criteria can be used to identify acute responders with more favourable outcome, a better prediction of prognosis may be achieved using other prognosticators also, such as the patient’s hemodynamic profile in addition to their acute response according the Sitbon criteria.

Acute vasodilator response criteria are designed for the purpose of identifying patients that respond well and sustained to CCB therapy, thereby distinguishing these patients from those that will not respond well and may even deteriorate on CBB therapy.
unknown which response criteria should be used to identify these sustained CCB responders. In chapter 4 we showed that in paediatric PAH there is a small subgroup of patients that have an excellent prognosis when treated with a CCB. Furthermore, we showed that this subgroup of patients can be identified by an acute vasodilator response according to the Sitbon criteria, whereas nonresponders according to the Sitbon criteria did not have an excellent outcome. Acute vasodilator testing using the Sitbon criteria in order to identify patients that respond well to CCB therapy is therefore an essential step in the treatment algorithm of paediatric PAH. The less strict REVEAL-paediatric criteria did not seem able to identify patients that have improved outcome when treated with CCB therapy. This data supports that in paediatric PAH acute responders, only according to the Sitbon-criteria, should be treated with CCB therapy.\textsuperscript{20}

Words of caution are however in order. Patients that initially are acute responders may lose the acute vasodilator response during their disease course and at that point should receive PAH-targeted therapy.\textsuperscript{17} Based on the current data one should treat paediatric IPAH/HPAH patients that are responders according to the Sitbon-criteria with CCB therapy and while doing so one should closely monitor these patients and consider PAH-targeted therapy at loss of acute vasodilator response or at clinical deterioration on CCB therapy. Data comparing acute vasodilator responders on CCB mono-therapy with patients receiving CCB in combination with PAH-targeted therapy is currently lacking. The question whether one should administer PAH-targeted therapy alongside CCB to prevent pulmonary vascular remodelling while lowering the right ventricular afterload can therefore not be answered at this time. Ideally a randomized trial comparing patients on CCB mono-therapy with patients on both CCB and PAH-targeted therapy would help us decide whether CCB therapy should be combined with PAH-targeted therapy when treating acute responders. Such a clinical trial would however be hampered by the limited number of acute responders that qualify for CCB therapy and the excellent outcome of these patients limiting the use of hard endpoints such as survival. Therefore to get this data an international study would be necessary to allow for the inclusion of sufficient patient numbers, while using a strong composite end-point that can represent clinical worsening.

After the first step, determining acute vasodilator response, the second step after diagnosis of PAH is to make a risk stratification by further determining the patient’s disease severity. This risk stratification is used to make optimal treatment decisions. Hemodynamic parameters historically have an important role in the evaluation of disease severity. Conventionally PAH patients are evaluated using mean pulmonary arterial pressure, pulmonary vascular resistance, cardiac output and mean right atrial pressure. These parameters however, do not provide a full representation of the right ventricular function and afterload, since they ignore the pulsatile properties of the pulmonary circulation.\textsuperscript{27,28}

The pulsatile properties of the pulmonary circulation are determined by pulmonary arterial compliance or stiffness and reflected pressure waves. The highly compliant pulmonary arteries of a healthy person are able to absorb the pulsatile pressure and flow waves emerging
from the right ventricle. Thereby the compliant arteries reduce the right ventricular afterload and workload. Furthermore, they protect the peripheral vascular bed from the steep pressure build-up of the pulsatile pressure load, that is regarded to be a stimulus for pulmonary vascular remodelling when increased. In pulmonary arterial hypertension stiffened pulmonary arteries have reduced compliance leading to an increased load on both the right ventricle and the peripheral vascular bed. Reflected pressure waves that in healthy subjects arrive at the right ventricle after pulmonary arterial valve closure are more early and powerful in pulmonary arterial hypertension, thereby increasing right ventricular afterload even further. Therefore, in contrast to the situation in healthy subjects, these pulsatile properties of the pulmonary circulation are believed to be important contributors to the right ventricular afterload in the diseased pulmonary vasculature of pulmonary arterial hypertension.29

These pulsatile properties can be defined by indices of pulmonary arterial stiffness, which are dynamic parameters that represent pulmonary arterial wall stiffening and compliance.29 Increased right ventricular afterload leads to an increased right ventricular work load, that eventually causes right ventricular failure. Since right ventricular failure is the main cause of death in pulmonary arterial hypertension, indices of pulmonary arterial stiffness may be able to evaluate disease severity and be predictive of outcome.

Several indices of pulmonary arterial stiffness had been introduced in the past, including pulmonary arterial capacitance (PACi), distensibility (D), dynamic compliance ($C_{dyn}$), pressure-strain modulus ($E_p$), stiffness index ($\beta_{ind}$), and stiffness coefficient ($\beta_{coeff}$).29-40 In chapter 5 we showed that invasively measured PACi is decreased in children with pulmonary arterial hypertension, compared to control patients.41 We also showed that the PACi is more severely decreased in patients with higher WHO-functional class (WHO-FC), which supports the relation of PACi with disease severity in these patients.41 And furthermore, a high PACi was associated with improved transplant-free survival. The latter confirms findings previously reported in adult PAH patients.30,32,33 In addition to PACi, the pulmonary stroke volume (PSVi) could be identified as a predictor of outcome in paediatric PAH, as had been previously reported in adults with the disease.42 These findings confirm that it is not only possible to invasively measure indices of pulmonary arterial stiffness, but also that these pulsatile parameters are able to help estimate disease severity and predict outcome in paediatric PAH. Furthermore, we showed that the associations of PACi and PSVi with outcome were stronger than that of mPAP and PVRi and independent from WHO-FC. In adult iPAH patients PACi was previously shown to be an independent predictor of outcome with stronger prognostic ability than conventional hemodynamic parameters.32,33 These findings indicate that indices of pulmonary arterial stiffness have complementary prognostic value to conventional prognostic parameters.

The invasively measured PACi represents the ability to accommodate oscillatory changes in volume of the pulmonary arterial tree as a whole. While it gives important insight in the pulsatile right ventricular afterload, it may be less suitable to represent the stiffness of the pulmonary arterial wall. The pulmonary arterial wall stiffness may be better represented
by locally measured parameters that use the transectional area or diameter change of the pulmonary arteries and relate them with the pressure differences in that pulmonary arterial segment. Several locally measured parameters, including the relative area change (RAC), distensibility and elastic strain index, either measured by transthoracic echocardiography or intravascular ultrasound were shown to be associated with outcome in paediatric and adult PAH.30,34,43

These commonly used definitions of indices of pulmonary arterial wall stiffness are obtained from minimal and maximal pressure and area or diameter measurements. Important characteristics of the pressure-area relationship may however lie in the continuous course of this relationship. Therefore the analysis of the entire course of the pulsatile pressure-area relationship of the pulmonary artery during a cardiac cycle may provide valuable additional information on pulmonary arterial stiffness. That is why in chapter 6 we introduced a new method to determine pulmonary arterial stiffness indices from continuous pulmonary arterial pressure-area loops. The theoretical advantages of using pulmonary arterial pressure-area loops to determine indices of pulmonary arterial stiffness over the traditional indices of pulmonary arterial stiffness are that compliance can be represented on a continuous scale and it provides pulmonary vascular wall velocity, timing parameters and a representation arterial wall viscoelasticity. Thereby a better characterization of pulmonary arterial stiffness may be achieved. Furthermore, the pressure build-up and timing may help characterize right ventricular function, enabling the evaluation of pulmonary arterial to right ventricular coupling.

In chapter 6 we demonstrated that we were able to measure indices of pulmonary arterial stiffness from pulmonary arterial pressure-area loops with low interobserver variability during routine right heart catheterization and transoesophageal echocardiography. We showed that it is feasible to use these loops to determine loop compliance during systole ($CL_{syst}$), loop compliance of the total cardiac cycle ($CL_{total}$) and elastance (EL) measured during diastole. Furthermore pulmonary arterial wall velocity, acceleration and acceleration time could be determined, which may represent pulmonary arterial stiffness (acceleration time) and hydraulic power during pressure build up (wall velocity). By determining the area within the pressure-area loop, pulmonary arterial wall dissipated energy was determined, which is a measure of pulmonary arterial wall viscoelasticity. The method described in chapter 6 is still work in progress. It has some imperfections causing a potential overestimation of the loop compliance, elastance and energy dissipation. We are currently working on improving our method to resolve these imperfections. Nevertheless, the feasibility of these measurements are promising and justify future studies further exploring these variables. For instance it would be valuable to study the possibility of determining pulmonary arterial to ventricular coupling using these new parameters. Focussing on the great advantages that easily obtainable non-invasive follow-up parameters would have for our patient population, developing a fully non-invasive method to measure these indices of pulmonary arterial stiffness would be of great interest. Furthermore, longitudinal follow-up and outcome studies would allow to
study the prognostic ability and changes of these parameters over time, whether induced by progression of disease or by treatment, so that eventually their potential value as treatment targets can be determined.

An increased right ventricular afterload leads to right ventricular dysfunction and eventually right ventricular failure. Since patients eventually die of right ventricular failure, right ventricular function is a determinant of outcome in PAH. Right ventricular (RV) function can be assessed using echocardiography, which is of major interest since echocardiography is widely available and non-invasive. Echocardiographic parameters of right ventricular function are therefore easy to obtain and feasible to perform repeatedly during follow-up. In chapter 7 we report that right ventricular dimensions and functional parameters, but also right atrial and left ventricular echocardiographic parameters are associated with disease severity and outcome in paediatric PAH, both at baseline and during follow-up.44 Therefore these easily obtainable echocardiographic parameters are determinants of outcome and may in the future be able to serve as parameters to guide treatment. Currently severe right ventricular dysfunction or enlargement determined by echocardiography is included in paediatric treatment recommendations as a determinant of high risk for worse outcome.16,45 Our data suggests that more echocardiographic parameters may be able to help provide a detailed risk stratification for paediatric PAH patients that can be valuable in making treatment decisions. But also our data confirms the relevance of right ventricular function as determinant of outcome.

As discussed above, echocardiographic evaluation of right ventricular function has a couple of advantages. It is non-invasive, relatively easy to perform, widely available and therefore suited for frequent repeated measurements during follow-up. However, despite these advantages, echocardiographic parameters are not yet widely used as treatment targets, which is due to a couple of disadvantages. For instance the right ventricle is not easy to visualize and does not lend itself for modeling of volume and ejection fraction and quantification of hypertrophy with echocardiography, because of its position, nongeometric shape and trabeculations.45 For that reason, it is common practice to subjectively assess right ventricular function and hypertrophy on echocardiographic images. Subjective measurements are prone to a low reproducibility and high interobserver variability, which impedes from gaining standardized echocardiographic treatment targets.

These disadvantages are overcome using other techniques. Cardiac magnetic resonance imaging (MRI) can provide multiple anatomic slices of the right ventricle during the different phases of a cardiac cycle, which allow for more reliable and reproducible volumetric analysis even in patients with an anatomic variant due to congenital heart disease.46-49 Furthermore cardiac MRI can be used to evaluate pulmonary blood flow, pulmonary arterial wave reflections and mechanical properties.45,50-52 Cardiac MRI parameters such as end diastolic right ventricular volume, stroke volume, and right ventricular mass have been shown to predict mortality in adult PAH.42 Data for pediatric PAH is limited but also shows prognostic relevance
of MRI measured parameters in children with pulmonary hypertension.\textsuperscript{53} In addition to cardiac MRI, computed tomography can be used to obtain functional and anatomic data, especially for patients in whom MRI is not feasible due to claustrophobia or metallic prosthesis or implanted devices.\textsuperscript{54} Computed tomography (CT) is furthermore able to provide additional prognostic parameters such as fractal branching.\textsuperscript{55} New echocardiographic techniques have also become available and may provide comparable functional data as CT and MRI. For instance 3 dimensional echocardiography can be used to determine right ventricular volume and ejection fraction in PAH and congenital heart disease patients, although it may underestimate right ventricular volumes compared to MRI.\textsuperscript{56-60} Furthermore, tissue Doppler echocardiography and speckle tracking can be used to determine right ventricular myocardial strain, strain rate and velocity, which may represent right ventricular function.\textsuperscript{61-64} MRI and CT have their disadvantages. MRI is time-consuming, costly and often requires narcosis in younger children, while CT is faster than MRI, requiring less patient compliance, but has the major disadvantage of radiation and contrast exposure. Three dimensional and tissue Doppler echocardiographic imaging do not have those disadvantages. At this moment there is not enough data on these imaging modalities in pediatric PAH to advice its use in routine evaluation and follow-up. In future, while more data becomes available on the prognostic abilities of right ventricular function parameters, the advantages of the different technical modalities must be weighed over their disadvantages. Considering that echocardiographic evaluation has the least disadvantages in patient risk, availability, obtainability and cost, it seems that most merit can be derived from improvement of 2 and 3 dimensional echocardiographic techniques. At least until such a time that MRI techniques have improved to an extent that they are less costly, and are either fast or correctable for patient movement so that narcosis in the younger child is no longer necessary.

Now we have discussed parameters that reflect right ventricular afterload and right ventricular function separately. However, both these entities are closely related. It is the increased right ventricular afterload that exerts an increased work load to the right ventricle, eventually leading to an impeded right ventricular function. But it is the right ventricle and its compensatory mechanism that determines pulmonary blood flow and cardiac output until lastly the right ventricular fails. It therefore seems obvious to not evaluate right ventricular afterload and function separately but together. It has been suggested that as long as the right ventricular function and right ventricular afterload are attuned to each other, or in other words coupled, a patient’s cardiac output can be retained. Uncoupling of the right ventricular function and afterload may be an important indicator of disease progression towards right ventricular failure to meet the demands of the high afterload.\textsuperscript{65-67} For future perspectives a measurement of right ventricular to arterial coupling, combining ventricular function and afterload data will be an interesting parameter for further study in paediatric PAH.

Besides right ventricular afterload and right ventricular functional parameters, physical functional levels and exercise capacity may be important parameters in the evaluation of the disease severity of patients with PAH. In chapter 8 we discuss the 6-minute walking distance
(6-MWD), which is a parameter that reflects submaximal exercise capacity. The 6-minute walking distance has long been used for adult PAH patients as an endpoint in multiple trials. However for paediatric PAH the prognostic abilities of the 6-MWD has not been clear and data reported is contradictory. Furthermore there have been concerns on the value of the 6-MWD in children since it cannot be performed in the very young, limiting its use to patients that are old enough to perform the test, and because it requires a fair amount of commitment of a child to perform a 6-MWD that actually reflect his or her exercise capacity. However, despite these potential disadvantages, we could show in chapter 8 that the 6-MWD reflects disease severity and moreover is an independent predictor of prognosis for children with PAH that are old enough (≥7 years of age) to reliably perform a 6-MWD test. Furthermore we were able to increase the 6-MWD ability to identify patients with worse outcome by adding the transcutaneous oxygen saturation (TcSO2) decrease during the 6-MWD as a second prognostic parameter. It is important to realize that, maybe more important than its prognostic capabilities, the 6-minute walking distance represents a patients ability to perform physical activity. Since quality of life is mostly determined by the patients well-being, independence and especially for children the ability to keep up with peers, the 6-minute walking distance is an important parameter in the evaluation of treatment effects in paediatric PAH as a direct measure of functional capacity, regardless of its relation with outcome. This is why also in the future the 6-MWD is a valuable tool to evaluate treatment effects in paediatric PAH.

It is important to realise that besides parameters obtained by a physician to evaluate disease progression, there can be other clinical signs indicating severe progressed PAH. In Chapter 9 we show that haemoptysis is an indicator of rapid deterioration to death or the need for lung transplantation. In adult PAH patients also detrimental outcome has been reported after haemoptysis. Therefore in PAH patients that suffered an episode of haemoptysis we need to be vigilant and re-evaluate our treatment strategy. The ESC guidelines on pulmonary hypertension state that haemoptysis is a potential contra-indication for anticoagulant therapy, implying that cessation of anticoagulant therapy needs to be considered after an episode of haemoptysis. In chapter 9 anticoagulant therapy could not be demonstrated a significant risk factor for haemoptysis. However, children who suffered from haemoptysis were more often treated with anticoagulants and a higher than generally accepted bleeding risk has been suggested in adult PAH patients on anticoagulant therapy. A risk-benefit analysis of anticoagulant therapy in PAH patients, based on prospective data, is necessary to elucidate whether cessation of anticoagulant therapy reduces the risk of recurrent haemoptysis. Furthermore, considering the high mortality after an episode of haemoptysis in both adult and paediatric patients urgent lung transplantations should be considered especially in patients that experienced life threatening haemoptysis.

After identifying determinants of outcome, the next step is to evaluate whether these parameters are suitable to determine the initial treatment and evaluate treatment effects during follow-up in order to make subsequent treatment decisions. Currently it is advised to treat PAH using a goal oriented treatment strategy, in which predefined treatment goals are used.
to evaluate whether a patient’s clinical condition improves during treatment. When those treatment goals are not met, therapy should be intensified by adding medication. Predictors of outcome are not automatically suitable to serve as treatment goals. Parameters that qualify to be treatment goals are either parameters that reflect a direct treatment benefit (such as improvement of functional capacity or quality of life) or are parameters that can function as surrogates for survival. Surrogate parameters for survival should have a strong association with survival, are able to change under the influence of treatment and those treatment-induced changes should reflect changes in outcome. In chapter 10 we used these criteria to identify surrogates for survival in a prospective standardized follow-up study. We found that WHO-FC, N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and tricuspid annular plane systolic excursion (TAPSE) adhere to these criteria and can serve as treatment goals in children with PAH. A large number of prognostic parameters could be tested in this study. However, not all parameters that were discussed in this thesis could be analysed. For instance, for the indices of pulmonary arterial stiffness, the lack of longitudinal data, impedes such analyses. The study of surrogates of survival that can serve as treatment goals requires long-term longitudinal follow-up data with standardised repeated measurements of the parameter of interest, data on treatment, adverse events and endpoints such as death. Large patient registries collecting all that data long term (in all patients) are however scarce, hampering the study of surrogates of survival. Recent initiatives such as the international TOPP2 registry will in future enable further analysis of potential treatment goals.

To conclude, several prognosticators were identified in the studies reported in chapters 3-10, including parameters that are surrogates for survival and can serve as treatment goals in a goal-oriented treatment strategy. It is thought that a goal-oriented therapy leads to more intensive therapy for those patients that have more severe or more rapidly progressive disease, which may further improve outcome in paediatric PAH. For adult PAH patients PAH-targeted add-on therapy has been demonstrated to induce clinical improvement. However, data on the effect of combination therapy on clinical condition and outcome of paediatric PAH patients was so far lacking. Before we can move on to a goal-oriented treatment strategy in children we should gain evidence to support that escalating therapy to combination therapy indeed has a beneficial effect.

**Treatment strategies**

The introduction of PAH-targeted therapies has led to an improved outcome for children with PAH. However, despite that improvement, contemporary survival rates for paediatric PAH are still unfavourable. Furthermore it has been reported that in both children and adults the clinical improvement achieved by treatment with a PAH-targeted drug, wears off over time. These findings are confirmed by our recent study presented in chapter 11, that showed a clinical deterioration after an initial clinical improvement in patients on bosentan mono-therapy. Furthermore, although randomised controlled trials in adult PAH patients show short-term improvement on PAH-targeted mono-therapy, there is a significant mortality,
treatment failure, clinical deterioration or need for additional therapies in patient on mono-therapy in long-term follow-up studies. This data indicates that important improvements in the treatment of PAH can still be achieved. Of course one of the ways to improve therapy of PAH is by further elucidating the molecular pathways that are involved in the development of PAH and right ventricular failure, in order to develop new medical therapies that target these pathways. However, while working on such new therapies, an improvement of current treatment strategies may be achieved.

From data on adult PAH we have learned that add-on combination therapy is clinically beneficial and may counter the effect of clinical deterioration during mono-therapy, shown by improving WHO-FC, 6MWD, haemodynamics, NT-proBNP and time to clinical worsening. For children a beneficial effect of add-on combination therapy had not been shown before. In chapter 11 we showed an improvement in WHO-functional class and 6-MWD after sildenafil add-on therapy in patients with a pre-defined clinical deterioration on bosentan mono-therapy. Considering that the 6-MWD and WHO-FC are both determinants of outcome in paediatric PAH (Chapters 8 and 12) and WHO-FC is identified to be a potential treatment target (chapter 10), this indicates that sildenafil add-on therapy improves disease severity in paediatric PAH. Furthermore in chapter 11 we showed that patients that had a more rapid deterioration on bosentan mono-therapy and therefore received sildenafil add-on therapy had better outcome compared to patients that remained on bosentan mono-therapy. In chapter 12 we found that patients that have been treated with PAH-targeted dual or triple therapy had a better survival compared to patients on PAH-targeted mono-therapy. Therefore to conclude, when using a PAH-targeted add-on therapy approach in paediatric PAH, putting patients on dual or triple therapy leads to an improvement of their outcome.

The beneficial effect of combination therapy on outcome in paediatric PAH makes one wonder if all patients should be treated with dual or triple PAH-targeted therapy upfront, directly after initial diagnosis. In the European Society of Cardiology (ESC) guidelines on pulmonary hypertension it is suggested that there is a rationale for upfront combination therapy, since the malignancy of the disease justifies aggressive pre-emptive combination therapy. Up-front combination therapy is however not yet advised due to a lack of data supporting its effectiveness. For future perspective, a long-term observational study comparing patients on upfront combination therapy to patients treated according to an add-on strategy may provide this data. However, such an observational method may be limited by a limited number of patients on upfront combination therapy, considering that this is currently not yet advised in treatment guidelines. More preferably a long term prospective randomised controlled trial comparing PAH targeted mono-therapy or add-on therapy with upfront combination therapy would provide important evidence in this matter.
Conclusion
The current thesis has addressed a number of thus far unmet needs in paediatric PAH and thereby will help to shape the future of paediatric PAH treatment. A summarizing overview of the epidemiology and clinical presentation of the paediatric pulmonary hypertension was given that will help to recognize and identify the disease in an earlier state, allowing for more early treatment initiation. The prevalence and current daily practice of acute vasodilator response testing was studied and it was shown that acute vasodilator response according to the Sitbon criteria is able to predict a patient’s prognosis and favourable response to calcium channel blocker therapy. A number of prognosticators for paediatric pulmonary arterial hypertension were identified, including acute vasodilator response, indices of pulmonary arterial stiffness, 6-MWD, TcSO2-decrease during 6-MWD, echocardiographic parameters and the occurrence of haemoptysis. Three parameters, WHO-FC, NT-proBNP and TAPSE, were shown to be prognostic and qualify to serve as treatment goals in paediatric PAH. A new method to determine indices of pulmonary arterial stiffness was developed using pulmonary arterial pressure-area loops that allow to analyse the continuous pulsatile pressure-area relationship. And furthermore we were able to show that sildenafil add-on therapy to bosentan mono-therapy improves disease severity and outcome. The benefit of combination therapy was further confirmed in a large international cohort study showing improved outcome for patients on combination therapy versus patients on PAH-targeted mono-therapy.

Future studies focussed on identifying treatment targets, evaluating the benefit of goal oriented and upfront combination therapy and trials to find new treatment agents targeting additional molecular pathways that are associated with PAH, will help to further improve outcome. And more importantly, these future studies may one day provide a cure to this progressive detrimental disease.
References


