Meaningful and feasible composite clinical worsening definitions in paediatric pulmonary arterial hypertension: An analysis of the TOPP registry

Maurice Beghetti a,*,1, Monika Brand b,1, Rolf M.F. Berger c,1, Tilman Humpl d, Jeremy G. Wheeler e,1, D. Dunbar Ivy f,1, Damien Bonnet g,1, on behalf of the TOPP investigators

a Paediatric Cardiology Unit, and Centre Universitaire Romand de Cardiologie et Chirurgie Cardiaque Pédiatrique, University of Lausanne and Geneva, Switzerland
b Global Medical Science and Epidemiology, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland
c Center for Congenital Heart Diseases, Department of Paediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
d Division of Cardiology, Hospital for Sick Children, University of Toronto, Toronto, Canada
e Quantitate Ltd, London, UK
f Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA
g M3C-Necker, Paediatric Cardiology, Reference Centre for Complex Congenital Heart Diseases, Hôpital Necker Enfants Malades, Université Paris Descartes, Paris, France

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Background: Composite clinical worsening (cCW) outcomes might allow measurement of disease progression in paediatric pulmonary arterial hypertension (PAH). This TOPP registry analysis investigated three cCW outcomes and their predictive strength for lung transplantation/death.

Methods: Patients ≤17 years with idiopathic/familial PAH or PAH-associated congenital heart disease diagnosed ≤3 months before enrolment were included. cCW outcomes included the following variables at enrolment and/or follow-up: all-cause death, PAH-related hospitalisation, lung transplantation, atrial septostomy (cCW1, 2 and 3), WHO FC deterioration, intravenous/subcutaneous prostanoids initiation, syncope (cCW2,3) and occurrence/worsening of ≥2 PAH symptoms (cCW3). The predictive value of CW (excluding transplantation and death) to transplantation or death was assessed. Predictive values of each cCW for lung transplantation/death were analysed by Cox proportional hazards models.

Results: From 255 patients, first-event rate/100 person-years (95% CI) were cCW1: 23.1(19.3,27.6), cCW2: 43.6 (37.6,50.6), and cCW3: 46.3(40.0,53.7) with PAH-related hospitalisation as the most frequent first event in each. The cCW definitions comprised from endpoints (excluding transplantation and death), were associated with higher risk [hazard ratio (95% CI)] for lung transplantation/death [4.23(2.27,7.91), 3.25(1.65,6.39), 2.74 (1.41,5.34), respectively]; individual parameters with higher risks were WHO FC deterioration [3.49 (1.47,8.29)], PAH-related hospitalisation [2.62(1.32,5.20)] and occurrence/worsening of ≥2 PAH symptoms [2.13(1.02,4.45)].

Conclusions: These data support the use of cCW outcomes in paediatric PAH research. WHO FC deterioration, PAH-related hospitalisation, occurrence/worsening of ≥2 PAH symptoms may be important for risk assessment during clinical management.

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1. Introduction

Paediatric pulmonary arterial hypertension (PAH) is a serious condition with significant morbidity and mortality, however prognosis has improved with the use of PAH-specific therapies approved for use in adults [1]. As there are multiple similarities between paediatric and adult patients with PAH [1–3], diagnostic and therapeutic algorithms used in adult PAH have been adopted, with some adaptations, for disease management in children, based on small-scale studies and expert opinion [3,4]. However, there are also important differences between
children and adults with PAH [1,3], therefore specific data for paediatric patients are required from real-world evidence and clinical trials.

To assess disease progression, or clinical worsening (CW), in the paediatric PAH population with the same outcome measure across all age ranges is more difficult than in adults. For example, 6-minute-walk distance (6MWD) that is widely used in adult PAH studies to measure exercise capacity is not a reliable outcome measure in paediatric studies of young children [3]. Right-sided heart catheterisation (RHC) is key at diagnosis and beneficial during follow-up in clinical practice for indications such as clinical deterioration, assessment of treatment effects, and listing for lung transplantation [1]; however, its use in paediatric clinical trials for the sole purpose of evaluating the efficacy of a drug is not supported given the risk involved with this invasive procedure [5]. These limitations of applying outcomes appropriate for adults to the paediatric population need to be overcome. Non-invasive clinical outcomes tailored for use in paediatric PAH are required in order to assess the efficacy of therapies in a clinical trial setting [6].

The use of composite CW outcomes is increasingly encouraged in PAH clinical research [7–9]. An evaluation of the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) found that a composite definition of time to clinical worsening, and its individual components, was highly predictive of death in adults [10]. Recent clinical trials of adult PAH therapies have used morbidity/mortality composite endpoints to demonstrate efficacy [11–13]. An observational study from a Dutch national referral centre including 70 patients reported on the predictive value of various composite CW definitions in paediatric PAH [14]. Therefore, we aimed to provide robust evidence that the use of composite endpoints might also be appropriate in paediatric PAH research if soft endpoints are revealed to be predictive of the hard endpoints lung transplantation and death.

Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) is a global, prospective, non-interventional registry conducted between January 2008 and July 2015. The registry was designed to provide information about demographics, disease course, treatment, and outcomes in paediatric pulmonary hypertension (PH) [15]. The objective of the current analysis of the TOPP registry was to evaluate the frequency of CW events using three different composite CW definitions in newly diagnosed (incident) children with PAH, and to determine the predictive values of these CW definitions as well as their individual components for lung transplantation or death in this population.

2. Methods

2.1. Study design and patient population

The design of TOPP has been reported in detail previously [15]. In brief, TOPP enrolled patients with WHO-confirmed PAH (World Symposium on Pulmonary Hypertension [WSPH] group 1) or (World Health Organization) WHO group 3–5 PH, aged from 3 months to 18 years, with increased pulmonary vascular resistance and normal left-sided filling pressures. The TOPP protocol was approved by the institutional review boards and ethics committees of the centres contributing to the registry. Patient and/or parental consent was obtained for all patients. The authors had full access to all data and agree to be accountable for its integrity and analysis.

The current analysis included solely incident (diagnosis ≥3 months before enrolment) patients aged ≥3 years at diagnosis and enrolment, with idiopathic PAH (IPAH), familial PAH (FPAH), familial PAH (FPAH) or PAH associated with congenital heart disease (APAH-CHD). Patients with APAH-CHD included those with an open, clinically significant, congenital systemic-to-pulmonary shunt (unrepaired, or repaired but with a substantial residual shunt), a corrected (closed) congenital systemic-to-pulmonary shunt, or with CHD that had never been repaired with a congenital systemic-to-pulmonary shunt (i.e. transposition of the great arteries flowing arterial switch) [15]. In addition, patients had to have at least one follow-up visit at any time after enrolment to be included in the analysis.

2.2. Variables

The following variables selected for the presented research were collected in the TOPP registry at enrolment and/or during follow-up: demographics (age, sex); disease characteristics: WHO functional class (WHO FC), presence/history, occurrence or progression of symptoms (dyspnoea, cyanosis, cough, fatigue, chest pain/discomfort, dizziness, near-syncpe); PAH-related hospitalisations (hospitalisations because of increased right-sided heart failure or haemoptysis); occurrence of syncpe; initiation of intravenous/subcutaneous prostanoids; atrial septostomy; lung transplantation; and death. The composite CW definitions included the disease variables summarised in Table 1 and named CW 1, 2, and 3. WHO FC deterioration was defined as a numerical increase of ≥1 FC, and, under this definition, patients classified as FC IV were not able to deteriorate further.

2.3. Statistical analysis

Descriptive statistics were used, including mean, SD, median, lower (Q1) and upper (Q3) quartiles, minimum and maximum for continuous variables, and counts and percentages for categorical variables. Rates for first events occurring after enrolment were calculated, where the denominator was time at risk, defined as person-years observation time until the first event. For the composite CW definition, the event rate per 100 person-years was calculated using the first event to occur among all the components. Kaplan-Meier estimates were conducted for time to first CW1, CW2, and CW3 events.

Factors predictive of lung transplantation or death were identified by Cox proportional hazards models. In order to evaluate the predictive value of the three CW definitions for lung transplantation or death, these two components were removed from the composite and these CW definitions were named CW1*, CW2*, and CW3*.

First, the individual component variables at diagnosis were assessed (Table 1: E, F, G, and H) in univariate models. Second, univariate and multivariate models of the first event of individual components (Table 1: C, D, E, F, G, H) were used. The survival time was determined in a time-dependent manner, starting at the time of the first event of the CW component. Multivariate models included only variables with p < 0.15 in the univariate models. A subgroup univariate analysis was conducted according to PAH aetiology (IPAH/FPAH and APAH-CHD). Statistical analyses were carried out using SAS v9.4 (SAS Institute, Cary, NC, USA).

3. Results

The analysis included 255 incident patients with PAH – 159 patients with IPAH/FPAH and 96 patients with APAH-CHD – from 34 centres in 20 countries (Supplemental material: Appendix). Patients were mostly female (60%) and had a median (Q1, Q3) age of 7 (3, 13) years at diagnosis. The WHO FC distribution at diagnosis was: FC I 33 (13%), FC II 109 (43%), FC III 87 (34%), and FC IV 24 (9%); two patients had missing WHO FC. The median (Q1, Q3) time between diagnosis and enrolment into TOPP was 0 (0, 1) months, and the median (Q1, Q3) observation time in TOPP was 33 (12, 55) months. At enrolment, 30 (12%) patients initiated intravenous/subcutaneous prostanoids. Presence/history of syncpe was reported in 22 (9%) patients once, in 34 (13%) patients several times, in four (2%) patients regularly, and the information was missing in two (1%) patients. Presence/history of ≥2 PAH symptoms was reported in 51 (20%) patients. Patient demographics and disease characteristics at enrolment for the two subgroups IPAH/FPAH and APAH-CHD are presented in Table 2.

Table 1 Composite clinical worsening definitions.

<table>
<thead>
<tr>
<th>Clinical worsening 1</th>
<th>Clinical worsening 2</th>
<th>Clinical worsening 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Death (all-cause)</td>
<td>(A) Death (all-cause)</td>
<td>(A) Death (all-cause)</td>
</tr>
<tr>
<td>(B) Lung transplantation</td>
<td>(B) Lung transplantation</td>
<td>(B) Lung transplantation</td>
</tr>
<tr>
<td>(C) PAH-related hospitalisation</td>
<td>(C) PAH-related hospitalisation</td>
<td>(C) PAH-related hospitalisation</td>
</tr>
<tr>
<td>(D) Atrial septostomy</td>
<td>(D) Atrial septostomy</td>
<td>(D) Atrial septostomy</td>
</tr>
<tr>
<td>(E) WHO FC deterioration</td>
<td>(E) WHO FC deterioration</td>
<td>(E) WHO FC deterioration</td>
</tr>
<tr>
<td>(F) Initiation of i.v./s.c. prostanoids (only first event)</td>
<td>(F) Initiation of i.v./s.c. prostanoids (only first event)</td>
<td>(F) Initiation of i.v./s.c. prostanoids (only first event)</td>
</tr>
<tr>
<td>(G) Syncpe</td>
<td>(G) Syncpe</td>
<td>(G) Syncpe</td>
</tr>
<tr>
<td>(H) Occurrence/worsening</td>
<td>(H) Occurrence/worsening</td>
<td>(H) Occurrence/worsening</td>
</tr>
</tbody>
</table>

≥2 PAH symptoms

a Increased right-heart failure, haemoptysis.

b Increase ≥1 WHO FC.

c Progression (in patients with symptom at enrolment) and occurrence/progression (patients without condition at enrolment) of ≥2 symptoms: dyspnoea (includes occurrence/progression at rest and progression with exertion in patients with condition at enrolment; and occurrence/progression of all dyspnoea in patients without symptom at enrolment), cyanosis, cough, fatigue, chest pain/discomfort, dizziness and near-syncpe (occurrence only).
Table 2
Patient demographics and disease characteristics at enrolment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPAH/FPAH (n = 159)</th>
<th>APAH-CHD (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>103 (65)</td>
<td>50 (52)</td>
</tr>
<tr>
<td>Median age at diagnosis (Q1, Q3), years</td>
<td>8 (3, 13)</td>
<td>5 (2, 12)</td>
</tr>
<tr>
<td>WHO FC, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (11)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>II</td>
<td>66 (42)</td>
<td>43 (45)</td>
</tr>
<tr>
<td>III</td>
<td>55 (35)</td>
<td>32 (33)</td>
</tr>
<tr>
<td>IV</td>
<td>19 (12)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Median observation period (Q1, Q3), months</td>
<td>33 (12, 50)</td>
<td>34 (14, 58)</td>
</tr>
<tr>
<td>Median time from diagnosis to enrolment (Q1, Q3), months</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>Initiation of I.V./s.c. prostanoids, n (%)</td>
<td>29 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>104 (66)</td>
<td>89 (93)</td>
</tr>
<tr>
<td>Once</td>
<td>17 (11)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Several times</td>
<td>32 (20)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Regularly</td>
<td>4 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Patients with presence/history ≥2 PAH symptoms, n (%)</td>
<td>39 (25)</td>
<td>12 (13)</td>
</tr>
</tbody>
</table>

Percentages are based on the number of patients (n) in the analysis set and groups/subgroups with non-missing data. APAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; IPAH/FPAH, idiopathic pulmonary arterial hypertension/familial pulmonary arterial hypertension; i.v., intravenous; PAH, pulmonary arterial hypertension; Q, quartile; s.c., subcutaneous; WHO FC, World Health Organization functional class.

The event rates per 100 person-years are summarised in Table 3. The first-event rate (95% confidence interval [CI]) for CW1 was 23.1 (19.3–27.6) per 100 person-years (121 events over 524.7 person-years). For CW2, the first-event rate almost doubled to 43.6 (37.6–50.6) per 100 person-years (173 events over 396.5 person-years) with the additional components E, F, G (WHO FC deterioration, initiation of intravenous/subcutaneous prostanoids and syncope; Table 1) added. The first-event rate for CW3 was 46.3 (40.0–56.7) per 100 person-years (175 events over 396.5 person-years) with the final component H (PAH symptoms; Table 1) added. The respective Kaplan-Meier estimate analysis showed that at 6, 12, and 18 months a first CW1 event (95% CI) was experienced by 23.6% (18.8–29.4), 31.5% (26.0–37.7), and 36.9% (31.1–43.5) patients, respectively; a first CW2 event was experienced by 30.1% (24.8–36.2), 41.7% (35.8–48.2), and 54.8% (48.6–61.5) patients, respectively; and a first CW3 event was experienced by 33.3% (27.8–39.5), 44.5% (38.5–51.0), and 57.3% (50.9–63.7) patients, respectively.

PAH-related hospitalisation was the most frequent first event in CW1, with a first-event rate of 17.9 (14.6–21.9) per 100 person-years, followed by all-cause death (3.0 (1.9–5.0) per 100 person-years) and PAH-related death (1.7 (0.8–3.3) per 100 person-years). PAH-related hospitalisation and WHO FC deterioration were the most frequent first events in CW2, with first-event rates of 17.9 (14.2–22.6) and 16.6 (13.1–21.2) per 100 person-years, respectively, and in CW3, with first event rates of 16.2 (12.6–20.8) and 15.4 (11.9–19.9) per 100 person-years, respectively. Atrial septostomy occurred as the first event in only one patient.

When evaluating factors predictive of lung transplantation or death in a univariate analysis, patients with WHO FC III at diagnosis were at increased risk of first event in the respective composite definition (Odds ratio 1.93, 95% CI 1.07–3.49; p = 0.03) (Table 4).

Table 3
Summary of composite clinical worsening definitions.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Clinical worsening 1 (N = 225)</th>
<th>Clinical worsening 2 (N = 225)</th>
<th>Clinical worsening 3 (N = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>121</td>
<td>173</td>
<td>175</td>
</tr>
<tr>
<td>Person-years</td>
<td>524.7</td>
<td>396.5</td>
<td>377.6</td>
</tr>
<tr>
<td>First-event ratea (95% CI)</td>
<td>23.1 (19.3–27.6)</td>
<td>43.6 (37.6–50.6)</td>
<td>46.3 (40.0–53.7)</td>
</tr>
</tbody>
</table>

First event in the respective composite definition

<table>
<thead>
<tr>
<th>Definition</th>
<th>n (95% CI)</th>
<th>n (95% CI)</th>
<th>n (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>16 (1.9–5.0)</td>
<td>14 (2.1–6.0)</td>
<td>14 (2.2–6.3)</td>
</tr>
<tr>
<td>PAH-related hospitalisation</td>
<td>9.1 (0.8–3.3)</td>
<td>8.2 (0.9–4.0)</td>
<td>8.2 (0.9–4.2)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>1.2 (0.0–1.1)</td>
<td>1.2 (0.0–1.4)</td>
<td>1.2 (0.0–1.5)</td>
</tr>
<tr>
<td>Atrial septostomy</td>
<td>1.2 (0.0–1.1)</td>
<td>1.3 (0.0–1.4)</td>
<td>1.3 (0.0–1.5)</td>
</tr>
<tr>
<td>Deterioration in WHO FC</td>
<td>–</td>
<td>66 (13.1–21.2)</td>
<td>58 (11.9–19.9)</td>
</tr>
<tr>
<td>Initiation of I.V./s.c. prostanoids</td>
<td>–</td>
<td>4 (0.3–2.6)</td>
<td>4 (0.3–2.7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>–</td>
<td>8.2 (0.9–4.0)</td>
<td>7.9 (0.7–3.8)</td>
</tr>
<tr>
<td>Occurrence/worsening ≥2 PAH symptoms</td>
<td>–</td>
<td>–</td>
<td>21.5 (3.6–8.5)</td>
</tr>
</tbody>
</table>

CI, confidence interval; I.V., intravenous; PAH, pulmonary arterial hypertension; s.c., subcutaneous; WHO FC, World Health Organization functional class.

a Rate per 100 person-years.
In the remaining analyses the survival time was defined in a time-dependent manner. In the univariate analysis of the first event of individual components (Table 1: C, D, E, F, G, H), WHO FC deterioration had the strongest predictive value for lung transplantation or death (HR, 6.70; 95% CI, 3.12–14.36), followed by occurrence/worsening of ≥2 PAH symptoms (HR, 4.77; 95% CI, 2.54–8.97), and initiation of intravenous/subcutaneous prostanooids (HR, 4.59; 95% CI, 2.13–9.87); all p < 0.0001 (Table 4). In multivariate analysis, a first event of WHO FC deterioration (HR, 3.49; 95% CI, 1.47–8.29), PAH-related hospitalisation (HR, 2.62; 95% CI, 1.32–5.20), and occurrence or worsening of ≥2 PAH symptoms (HR, 2.13; 95% CI, 1.02–4.45) were significant independent risk factors for lung transplantation or death (Table 4).

All three CW definitions (excluding the components lung transplantation and death) were associated with a significantly higher risk for lung transplantation or death (Table 4).

Predictive models for lung transplantation or death according to aetiology are shown in Supplementary Table 1. For the subgroup of patients with IPAH/FPAH (n = 159), the univariate and multivariate analyses found results similar to those in the overall population. However, for the subgroup of patients with APAH-CHD (n = 96), none of the CW definitions or individual components were significant predictive factors for lung transplantation or death (Supplementary Table 1).

4. Discussion

The current analysis, using data from the TOPP registry, a large cohort of paediatric patients with PAH, primarily aimed to create and determine the predictive value of a CW endpoint (including death and transplantation) that could be used in clinical trials. The analysis also describes the relevance of composite CW definitions (excluding death and transplantation) to predict lung transplantation or death, which could be used for future prognostic studies and to identify patients with a higher risk of disease progression. The CW definitions comprised a combination of disease variables. All-cause death, PAH-related hospitalisation (owing to increased right-sided heart failure or haemoptysis), lung transplantation, and atrial septostomy were included in all three CW definitions, with the addition of WHO FC deterioration, initiation of intravenous/subcutaneous prostanooids and syncope to CW2 and CW3, and occurrence or worsening of ≥2 PAH symptoms to CW3. These CW definitions were designed to evaluate the differences in the proportion of events during follow-up when more subjective clinical outcomes were introduced into the definition. Furthermore, this analysis assessed the predictive value of the individual disease variables and the CW definition (excluding lung transplantation and death) for lung transplantation or death.

Our first interesting result is that the number of events in a paediatric cohort of PAH is high regardless of the CW definition used. As expected, the number of events increases when more subjective clinical outcomes are included in the CW definition. The observed event rate, ranging from 23.1 to 46.3 per 100 person-years is consistent with an earlier study of 70 patients with paediatric PAH that showed the number of clinical events was high in the study population, when considering a composite definition of death, lung transplantation, PAH-related hospitalisation, initiation of intravenous prostanooids and functional deterioration (WHO FC and/or 6MWD) [14].

The second interesting result is the frequency of first CW event, in this population of incident patients. This high frequency of events and their precocity are valuable information for designing future trials as paediatric PAH is a rare and heterogeneous disease, and reducing the need for large cohorts of patients to evaluate the efficacy of a new compound or treatment strategy is a crucial issue. Knowing the frequency and timing of CW events is important information for sample size calculation of future trials.

The third notable finding generated by the current study is the predictive value of individual disease variables WHO FC deterioration, PAH-related hospitalisation, and the occurrence or worsening of ≥2 PAH symptoms. These three variables were predictive of lung transplantation or death in both the univariate and multivariate models. These findings are consistent with and expand upon the results of the national Dutch cohort study that found FC deterioration to be predictive of lung transplantation or death in paediatric PAH [14,16]. They are also in agreement with an analysis of adult patients with PAH that found reduced survival in patients with unchanged or worsened WHO-FC compared with patients whose WHO FC improved [17]. Furthermore, the results from the current analysis provide evidence for the first time that the occurrence or progression of ≥2 PAH symptoms is predictive of lung transplantation or death in paediatric PAH. We also show here that PAH-related hospitalisation was the most frequent first event in the CW definitions, similar to the findings in adult PAH trials that have used composite morbidity/mortality endpoints including PAH-related hospitalisation. Hospitalisation for PAH deterioration is certainly an important factor as mortality is higher in paediatric patients who are hospitalised for PH compared with general paediatric hospitalisations [18]. An analysis of the REVEAL cohort found first PAH-related hospitalisations to be more frequent in adult than paediatric PAH patients, and predictive of subsequent rehospitalisation and poorer 3-year survival [19]. It is of note that the paediatric REVEAL analysis included mainly prevalent patients diagnosed during childhood. The current study only included incident patients; therefore, our findings are potentially more robust for predicting long-term outcomes, as the impact of a survival bias is minimised compared with prevalent cohorts.

Syndrome was not found to be predictive of lung transplantation or death in this cohort, which is in line with results of previous cohort studies [20,21]. Recently, in a small study of 55 paediatric patients with PAH, although the absence of syncope was linked to improved prognosis, the presence of syncope was not considered to be a risk factor for lung transplantation or death [22]. We believe that this information has a clinical importance for the decision to escalate therapy. Indeed, the practice of prescribing an additional drug or recommending a paediatric patient for lung transplantation when syncope recures should certainly be reviewed in the light of these findings.

Composite CW endpoints have been adopted in recent clinical trials of adult PAH therapies as morbidity/mortality endpoints [11–13], and their use is being encouraged in paediatric PAH clinical trials [2,5,23]. Analysis of composite CW endpoints has always been a challenge because of the lack of a standardised definition [24,25]. The current study evaluated the relevance of three different definitions. Interestingly, all three CW composite outcomes were significantly predictive of lung transplantation or death. This was in agreement with the findings of a recent cohort study of paediatric patients in the Netherlands [14]. These current analyses may inform the design and sample size calculation of future paediatric PAH trials and support the use of a composite CW endpoint in those trials. Indeed, the first paediatric trial incorporating these composite endpoints in the design was initiated in 2017 [26].

Compared with results in the overall population, similar results were observed in the subgroup of patients with IPAH/FPAH, with an even greater predictive value of lung transplantation or death for several of the individual disease variables (Supplementary Table 1). Conversely, no significant predictors of lung transplantation or death could be identified in the APAH-CHD subgroup. However, this subgroup included heterogeneous underlying CHD physiologies and the number of outcome events was small, which contributed to the wide CIs. Indeed, patients with Eisenmenger physiology have different survival outcomes than those with a closed shunt and PAH [27–29]. Identifying specific predictors in subsets with APAH-CHD would require large patient numbers and, potentially, other factors in the predictive model, such as the type of shunt (pre- or post-tricuspid), and the type of underlying CHD.

The findings of the current study define a clinical endpoint for further use in clinical trials. A PAH worsening definition based on occurrence or progression of symptoms may be predictive for death and lung transplantation, and therefore could be used for prognostic studies.
and in clinical practice to identify patients at higher risk of disease progression and poorer outcomes. The current study identified the occurrence of symptoms as a reliable predictor of outcomes in paediatric PAH. The different CW definitions may be useful for risk stratification of a patient during follow-up.

4.1. Limitations

There are certain limitations to this study inherent to observational studies. Further analyses are warranted including analysis for competing risks, adjustment for treatment patterns and other potential confounders. Such additional analysis could be considered based on an updated cohort from the TOPP registry as well as from controlled clinical trials. The study only defined PAH worsening and not PAH improvement. This information would have been important to further guide the management of these patients in clinical practice, and to facilitate the design of future paediatric PAH trials. Similarly, therapeutic targets were not confirmed in this cohort. These targets are scarcely identified in paediatric PAH [16]. The Dutch cohort found that improvements in WHO FC, N-terminal brain pronatriuretic peptide, and tricuspid annular plane systolic excursion after treatment are associated with better survival [16]. The learnings from the TOPP-1 registry have informed the design of future paediatric PAH trials. Similarly, therapeutic targets for treatment goals that were proposed at the 2013 World Symposium on PH [1], as well as to identify new treatment goals. This database will focus more on the collection of follow-up variables, such as NT-proBNP, which have become important for risk assessment in recent years and may provide further analysis of the associations between these variables and clinical endpoints.

5. Conclusions

The results from this analysis of the TOPP registry suggest that different CW definitions could be used as primary endpoints in future paediatric PAH trials and prognostic studies. Indeed, the number of events according to the different definitions is high and the events occur early in the course of the disease, suggesting that the number of patients needed to be included in randomised control trials could be reduced compared with the event-driven trials in adult PAH [12,31]. In addition, WHO FC deterioration, PAH-related hospitalisation, and occurrence or worsening of ≥2 PAH symptoms are predictive of lung transplantation or death. These findings are of importance for individual monitoring as well as for the individual risk assessment and therapeutic decisions during follow-up in paediatric PAH patients.

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Disclosures

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Appendix A. Supplementary data

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