Pulmonary hypertension in Switzerland: treatment and clinical course

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Abstract

Background: The prognosis of pulmonary hypertension (PH), especially idiopathic pulmonary arterial hypertension (IPAH), has improved during the recent years. The Swiss Registry for PH represents the collaboration of the various centres in Switzerland dealing with PH and serves as an important tool in quality control. The objective of the study was to describe the treatment and clinical course of this orphan disease in Switzerland.

Methods: We analyzed data from 222 of 252 adult patients, who were included in the registry between January 1999 and December 2004 and suffered from either PAH, PH associated with lung diseases or chronic thromboembolic PH (CTEPH) with respect to the following data: NYHA class, six-minute walking distance (6-MWD), haemodynamics, treatments and survival.

Results: If compared with the calculated expected figures the one, two and three year mean survivals in IPAH increased from 67% to 89%, from 55% to 78% and from 46% to 73%, respectively. Most patients (90%) were on oral or inhaled therapy and only 10 patients necessitated lung transplantation. Even though pulmonary endarterectomy (PEA) was performed in only 7 patients during this time, the survival in our CTEPH cohort improved compared with literature data and seems to approach outcomes usually seen after PEA. The 6-MWD increased maximally by 52 m and 59 m in IPAH and CTEPH, respectively, but in the long term returned to or below baseline values, despite the increasing use of multiple specific drugs (overall in 51% of IPAH and 29% of CTEPH).

Conclusion: Our national registry data indicate that the overall survival of IPAH and presumably CTEPH seems to have improved in Switzerland. Although the 6-MWD improved transiently, it decreased in the long term despite specific and increasingly combined drug treatment. Our findings herewith underscore the progressive nature of the diseases and the need for further intense research in the field.

Key words: chronic thromboembolic pulmonary hypertension; endothelin receptor antagonists; bosentan; haemodynamics; idiopathic pulmonary arterial hypertension; New York Heart Association; phosphodiesterase-5 inhibitors; sildenafil; prostamids; ilomedin; pulmonary hypertension; registry; 6-minute walking distance; survival; treatment

Abbreviations

CTEPH Chronic thromboembolic pulmonary hypertension
IPAH Idiopathic pulmonary artery hypertension
NYHA New York Heart Association
PAH Pulmonary arterial hypertension
PEA Pulmonary endarterectomy
PH Pulmonary hypertension
6-MWD 6-minute walking distance
SVO2 Mixed venous oxygen saturation

Financial support: The Swiss Society for Pulmonary Hypertension received financial support from Actelion Switzerland to run the registry.
Introduction

Pulmonary hypertension (PH) comprises a group of orphan diseases with a poor prognosis if untreated. The revised Venice classification [1] includes pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) as the main classes that intrinsically affect the pulmonary circulation thereby distinguishing them from PH due to left heart disorders or chronic hypoxaemia. PAH is histologically characterized by proliferation and myofibrotic remodelling of small pulmonary artery vessel walls and can be subdivided into idiopathic (IPAH) and familial PAH, such as PAH associated with other conditions (collagen vascular disease, congenital heart disease, portal hypertension, HIV infection, drug or substance abuse). CTEPH can affect the proximal or distal pulmonary arteries. Patients with a proximal CTEPH can be treated by pulmonary endarterectomy (PEA) [2]. This highly complex operation is performed only in a few centres worldwide and in Switzerland, it has only recently become available in collaboration with the German centre. However, CTEPH may share common vasoreactivity properties with PAH and hence be amenable to vasodilator treatment [3].

Before the availability of specific therapy, the median survival of IPAH was 2.8 years, with one and three year survival of 68% and 48% [4]. Based on these data from the US registry an equation including the pulmonary artery pressure, right atrial pressure and cardiac index was developed to predict survival (NIH formula).

Since the introduction of intravenous epoprostenol in 1995, the 1 and 3 year survival rates have increased to 88% and 68%, respectively [5]. Epoprostenol treatment, however, was limited by the necessity of continuous intravenous infusion through a central venous line prone to various complications and therefore has rarely been used in Switzerland [6]. Advances in diagnosis and new therapeutic options including inhaled iloprost [7], oral bosentan [8] and sildenafil [9] have created an increased interest in PH.

The first report from the Swiss Registry on patients with PH in Switzerland dates from 2001 [6]. In this article we present an update on treatment, clinical course and survival of patients with PH in Switzerland.

Material and methods

The Swiss PH Registry was opened in 1999 and includes prospective patient data from nine Swiss Hospitals (all five university hospitals and four cantonal hospitals). All patients provide written informed consent. PH is defined as a mean pulmonary artery pressure (mPAP) of >25 mm Hg at rest or >30 mm Hg at exercise, and a pulmonary arterial occlusion pressure >15 mm Hg [10]. According to the current clinical classification [1] patients are grouped in the following classes: 1. PAH 2. PH due to left heart disease 3. PH associated with chronic lung disease, 4. CTEPH, 5. PH due to miscellaneous disorders. The following data were collected: age, gender, diagnosis according to the clinical classification [1], date of PH diagnosis, height, weight, blood pressure, heart rate and oxygen saturation at rest, NYHA class, six-minute walking distance (6-MWD), haemodynamics assessed by right atrial pressure (RAP), mixed venous oxygen saturation (SvO₂), current medication and survival.

For the present paper, we analyzed data from 252 adult patients (>18 years of age) who were included in the registry between January 1999 and December 2004. Of these, 30 patients were excluded for the following reasons: (1.) patients with PH due to left heart disease (as this registry focuses on precapillary PH, n = 2), (2.) patients with various rare medical conditions (class 5) (n = 9), and (3.) patients without follow-up data (n = 19). Thus, overall data from 222 patients were available for analysis (figure 1). Data collection included patients providing data at the following three time points: 1. the first visit of the patient (baseline = BL), 2. the visit at the time of the best 6-MWD (best), as the 6-MWD is used as the primary endpoint in most clinical trials in PH and we hoped to obtain some information about the maximal achievable improvement under therapy, and at the last visit (last). Patients’ survival was completed at the time of death, or censored at the time of the last observation, pulmonary endarterectomy (PEA) or transplantation. We compared survival observed in the subset of 76 IPAH patients with the expected survival calculated for each patient based on the NIH formula [4]. This US national prospective trial with 194 patients with idiopathic PH estimates from a proportional hazards model, an equation to predict a patient’s chance of survival. This NIH formula is calculated as follows: P(t) = [F(t)]^\exp(-\lambda(x,y,z)), where \lambda(x,y,z) = EXP (0.007325x+0.0526y–0.3235z), x is mean pulmonary artery pressure, y is mean right atrial pressure, and z is cardiac index. The probabilities of survival at 1, 2,
and 3 years are given by the following: \( P(1) = 0.75 \); \( P(2) = 0.65 \); and \( P(3) = 0.55 \).

All results are expressed as means (standard deviations). Statistical analysis was performed using SPSS version 12.0.1 software package. The paired T-test was used for continuous variables and the Chi square test for discrete variables. Kaplan-Meier statistics was used to estimate overall survival. A p value <0.05 was considered to be significant.

**Results**

The baseline characteristics of the 222 patients included in the current analysis are shown in table 1. The mean follow-up was 24 (17) months (range 1–70). The time between the baseline and the best values was 12 (13) months, and the time between best and last values 12 (13) months. Mean age was 57 (16) years and 60% of the patients were female. The mPAP was not significantly different in patients with IPAH and those with CTEPH [51 (18) respectively 46 (13)]

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 222)</th>
<th>IPAH (n = 76)</th>
<th>CTEPH (n = 66)</th>
<th>CVD (n = 33)</th>
<th>HIV (n = 10)</th>
<th>Lung (n = 17)</th>
<th>Others (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (SD)</td>
<td>57 (16)</td>
<td>55 (17)</td>
<td>63 (13)</td>
<td>57 (15)</td>
<td>44 (13)</td>
<td>63 (11)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Female sex (n)</td>
<td>134 (60%)</td>
<td>52 (68%)</td>
<td>37 (56%)</td>
<td>23 (70%)</td>
<td>4 (40%)</td>
<td>6 (35%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Body mass index in kg/m² (SD)</td>
<td>26 (7)</td>
<td>27 (8)</td>
<td>26 (5)</td>
<td>24 (5)</td>
<td>21 (3)</td>
<td>26 (4)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>NYHA functional class (n)</td>
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<tr>
<td>- Class I</td>
<td>1 (0.5%)</td>
<td>1 (1%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Class II</td>
<td>24 (11%)</td>
<td>7 (8%)</td>
<td>9 (14%)</td>
<td>3 (9%)</td>
<td>2 (12%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>- Class III</td>
<td>144 (65%)</td>
<td>51 (71%)</td>
<td>46 (61%)</td>
<td>20 (61%)</td>
<td>1 (10%)</td>
<td>8 (47%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>- Class IV</td>
<td>53 (23%)</td>
<td>16 (21%)</td>
<td>17 (25%)</td>
<td>9 (27%)</td>
<td>9 (90%)</td>
<td>7 (41%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>6-MWD in m (SD)</td>
<td>356 (142)</td>
<td>335 (139)</td>
<td>364 (146)</td>
<td>359 (157)</td>
<td>395 (109)</td>
<td>311 (146)</td>
<td>351 (139)</td>
</tr>
<tr>
<td>mPAP in mm Hg (SD)</td>
<td>49 (17)</td>
<td>51 (19)</td>
<td>46 (13)</td>
<td>44 (13)</td>
<td>48 (10)</td>
<td>47 (15)</td>
<td>64 (23)</td>
</tr>
<tr>
<td>RAP in mm Hg (SD)</td>
<td>9 (7)</td>
<td>10 (8)</td>
<td>10 (6)</td>
<td>7 (5)</td>
<td>6 (4)</td>
<td>7 (4)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>CO in L/min (SD)</td>
<td>4.1 (1.3)</td>
<td>4.2 (1.3)</td>
<td>3.7 (1.8)</td>
<td>4.0 (1.1)</td>
<td>3.9 (1.2)</td>
<td>4.5 (1.0)</td>
<td>5.1 (2.0)</td>
</tr>
<tr>
<td>SVO2 in % (SD)</td>
<td>59 (11)</td>
<td>61 (10)</td>
<td>58 (7)</td>
<td>58 (16)</td>
<td>59 (6)</td>
<td>55 (18)</td>
<td>64 (8)</td>
</tr>
</tbody>
</table>

IPAH: Idiopathic pulmonary artery hypertension, CTEPH: Chronic thromboembolic pulmonary hypertension, CVD: Collagen vascular disease, HIV: Human immunodeficiency virus infection, Lung: Pulmonary Hypertension associated with lung diseases and/or hypoxia. Others: Other causes of pulmonary artery hypertension, NYHA: New York Heart Association, 6-MWD: 6-minute walking distance, mPAP: mean pulmonary artery pressure, RAP: mean right atrial pressure, CO: mean cardiac output, SVO2: mixed venous oxygen saturation

Data are given as means, standard deviation (SD) and percentages (%).
mm Hg; \( p = 0.16 \). During the observation period, 147 patients survived, 10 underwent lung transplantation, 7 PEA and 58 died. The 1, 2, 3 and 5 year survival of the whole population was 85%, 74%, 71%, and 53%, respectively. There was no difference in survival between patients with PAH, CTEPH or patients with lung diseases (figure 2). Compared with IPAH, patients suffering from PAH associated with connective tissue diseases and HIV had a significantly worse survival (\( p = 0.034 \) and \( p = 0.027 \), respectively).

When compared to the expected survival calculated according to the NIH formula, the 1, 2, and 3 year mean survival for patients with IPAH increased from 67% to 89%, from 55% to 78% and from 46% to 73% and was comparable with other investigated cohorts (figure 3) [5, 12]. For further analysis concerning treatment, only the major patient groups IPAH (n = 76) and CTEPH (n = 66) were included. At baseline, most patients were in NYHA class III (65%) and IV (24%) with no difference between the two groups. Follow-up data of patient allocation to NYHA classes are shown in table 2. Initially, medical care seemed effective, a significant improvement from baseline to best with more IPAH patient being in NYHA class I or II compared to III was found (\( p = 0.025 \)). In the long term, patients seemed to either respond or not respond to therapy, as the number of NYHA class III patients decreased significantly from baseline to the last visit at the expense of class II (therapy-responders) and class IV (non-responders). There was a similar trend in CTEPH, although it seemed that the percentage of non-responders was somewhat higher in this group (table 2).

Therapy seemed also to be effective initially as regards exercise capacity measured by the 6-MWD, which significantly increased from baseline to best in both IPAH and CTEPH (\( p < 0.001 \) for both groups, figure 4). However, this considerable improvement could not be maintained in the long-term as the 6-MWD declined to baseline values in both groups (\( p > 0.001 \) between best and last, \( p = ns \) between baseline and last for all groups, figure 4).

Treatments are divided into basic (oxygen, diuretics, oral anticoagulation) and PH-specific (prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors) as well as into...
uretics, oral anticoagulation) and PH-specific (prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors) as well as into single (only one specific drug) and multiple (more than one specific drug) medications.

The basic treatment at all time points is shown in Table 3. Basic therapy was broadly applied in all groups. At the last visit 40% of all patients (IPAH + CTEPH) were on oxygen, 54% on diuretics and 87% on oral anticoagulation, with no major differences between the groups. In the CTEPH group all but one (haemophilia patient, 65/66) were receiving oral anticoagulation at their last visit. From baseline to the time of the best 6-MWD there were marked increases in the use of oxygen, diuretics and oral anticoagulation in all groups.

The percentage of patients receiving specific therapy significantly increased from baseline to the last visit; from 31% to 89% in patients with IPAH and from 31% to 81% in CTEPH. The overall number of patients receiving each of the five specific treatment modalities including multiple therapies is shown in Table 4.

Regarding the drugs used for single specific therapy, there was a tendency towards a decreased use of inhaled iloprost over time in both group and a tendency towards an increased use of bosentan in CTEPH patients.

From baseline to best, respectively last visit, there was a steady increase in the use of multiple specific drugs (from 4% to 29% respectively 51% in IPAH patients, and from 4% to 16% respectively 29% in CTEPH patients). Considering the various combination treatments (Table 4), the most frequently applied combination in IPAH was inhaled iloprost with bosentan and in CTEPH inhaled iloprost with sildenafil. More than a quarter of the IPAH patients were on three or more drugs at the last visit.

### Discussion

The present study summarizes the therapeutic management and clinical course of PH patients from the Swiss registry. The overall survival in the present PH cohort was 71% at three and 53% at five years. Whereas survival of patients with IPAH and CTEPH as well as those with PH associated with lung diseases was comparable, prognosis of PAH associated with connective tissue diseases and HIV infection was significantly worse. This is in line with the previously published cohorts. In a recent series of 91 patients receiving continuous intravenous epoprostenol treatment, the 3-year

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>IPAH</th>
<th>CTEPH</th>
<th>IPAH</th>
<th>CTEPH</th>
<th>IPAH</th>
<th>CTEPH</th>
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<tr>
<td>Oxygen (%)</td>
<td>25</td>
<td>22</td>
<td>33</td>
<td>36</td>
<td>59</td>
<td>79</td>
</tr>
<tr>
<td>Best</td>
<td>41†</td>
<td>30</td>
<td>43</td>
<td>55*</td>
<td>84**</td>
<td>89</td>
</tr>
<tr>
<td>Last</td>
<td>42</td>
<td>38</td>
<td>49</td>
<td>61</td>
<td>84</td>
<td>98</td>
</tr>
</tbody>
</table>

IPAH: Idiopathic pulmonary artery hypertension, CTEPH: Chronic thromboembolic pulmonary hypertension, OAK = oral anticoagulation. *p <0.05; **p <0.001

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>IPAH</th>
<th>CTEPH</th>
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<tbody>
<tr>
<td></td>
<td>BL</td>
<td>Best</td>
</tr>
<tr>
<td>Specific Therapy*</td>
<td>26 of 83</td>
<td>63 of 75</td>
</tr>
<tr>
<td>Single-drug</td>
<td>CCB (%)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Bo inh (%)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Bo iv (%)</td>
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<tr>
<td></td>
<td>Bos (%)</td>
<td>30</td>
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<tr>
<td></td>
<td>Sil (%)</td>
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<tr>
<td>Multiple drugs</td>
<td>Bos+Sil (%)</td>
<td>0</td>
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<tr>
<td></td>
<td>Bos+Bo (%)</td>
<td>4</td>
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<tr>
<td></td>
<td>Bos+Sil (%)</td>
<td>0</td>
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<td></td>
<td>3 and &gt; (%)</td>
<td>0</td>
</tr>
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IPAH: Idiopathic pulmonary artery hypertension, CTEPH: Chronic thromboembolic pulmonary hypertension, BL = Baseline, CCB: Calcium Channel Blocker, Bo inh: Ilomedin inhalation, Bo iv: Ilomedin intravenous, Bos: Bosentan, Sil: Sildenafil, * Overall number of patients on specific drug therapy
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In an Israeli study on IPAH patients most were on anticoagulation at the first registration (95% vs. 59% in our study) but only 13% were already treated with prostacyclins (compared with 20% in our study) [26]. At baseline, 31% of the IPAH patients were on specific drug medication (20% on prostaglandins and 9% on bosentan). These data differ from a large American cohort on patients with PAH, where 31% of patients were on calcium channel blockers at the time of referral and only a small number on prostaglandins (2.4%) or bosentan (3.1%) [27].

Our favourable survival data might be explained by the introduction of specific vasodilator combination therapy. As shown in figure 4, after one year of treatment the 6-MWD improved by 52m and 59m in IPAH and CTEPH, respectively. These figures are comparable to those reported in the recent large randomized trials [7–9, 28]. After another year, however, the 6-MWD had decreased to the baseline levels, emphasizing the fact that these disorders exhibit a relentlessly progressive nature. At this time point more than half of the IPAH patients and almost one third of those with CTEPH were on combination therapy, predominantly inhaled iloprost and bosentan in IPAH, and inhaled iloprost and sildenafil in CTEPH of patients. So far, there are numerous case series of mainly PAH patients demonstrating a potential benefit of vasodilator combination therapy [29–33]. After the first randomized trial of bosentan added on to intravenous epoprostenol failed to show a benefit [34], probably due to the insufficient number of patients included, a recent randomized study on the addition of inhaled iloprost to bosentan revealed a significant improvement in the 6-MWD, a decrease in NYHA functional class and a delayed time to clinical worsening in the treatment group [35].

Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with PH [25] but there are no data showing that long-term supplemental oxygen is beneficial in pulmonary hypertension with or without hypoxaemia. At the last time point 42% of our IPAH patients were on oxygen therapy. This is rather a high number compared with Breathe-1 (33%) and STRIDE-1 (30%). There may be an overuse in Switzerland and this must be better monitored. Available data on drug treatment based on pulmonary hypertension registries are very limited.
the 532 patients who underwent PEA at the world’s largest centre in San Diego [38].

The present study based on national registry data has a number of limitations. As noted in the methods section one of our chosen time point is the “best 6-MWD”. This is somewhat arbitrary and might favour statistically significant results between this point and BL or the last visit. However, it was our intention to gain insight into the maximal possible therapeutic effect. Therefore we choose the 6-MWD as the most widely used endpoint of clinical trials. This enables us to compare our registry data, which are likely to represent ordinary clinical practice, with the results of randomized controlled trials in the field. The selection of the time of the best 6-MWD as a further data point also provided us with an additional and more complete data set. This would not have been the case if we had chosen another fixed time point (e.g. one year after therapy). Although prospectively entered, registry data collection is not scheduled prospectively as in proper clinical trials but reflects every day clinical practice where patients are scheduled based on the well being, illness, social and occupational availability of both patients and health care providers. Therefore, registry data might be flawed by missing or inconsistent parameters. In comparison with clinical trials, every patient with the disease can be entered in the registry regardless of co-morbidities. However registry entering is voluntary and therefore some PH-patients might be unidentified. Summarizing the drawbacks and advantages, we believe that nation wide registry data including a broad patient collective (presumably also multi- or comorbid patients, who would never be entered in a randomized study) provide important information for health care providers in the field.

In conclusion, these data retrieved from the Swiss PH Registry describe the management of patients with PH in Switzerland with emphasis on the major groups IPAH and CTEPH. They indicate an improvement in prognosis of these patients in the recent years, including a low percentage of patients necessitating intravenous prostaglandin therapy or lung transplantation. Interestingly, patients with CTEPH exhibited a similar improvement in prognosis under standard vasodilator therapy. Our findings encourage the thorough maintenance and complementation of the Swiss PH registry in order to acquire high quality surveillance data of PH patient care in the future.

The authors are indebted to Ulla Tredler, R.N. for her continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland, for their continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland, for their continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland, for their continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland, for their continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland, for their continuing efforts in maintaining the high data quality of the registry, Actelion, Baden, Switzerland.

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