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Original Research Article

Pulmonary Circulation

Pulmonary arterial hypertension associated with congenital heart disease: lessons learnt from the large Turkish Nationwide Registry (THALES)

Serdar M. Kücükoglu[1], Cihangir Kaymaz[2], Dursun Alehan[3], Serdar Kula[4], Atıf Akcevin[5], Alpay Celiker[6], Sertac M. Cicek[7], Lale S. Tokgözoglu[8] and Suleyman Kentli[9]; On behalf of THALES Registry Investigators

[1]Department of Cardiology, Istanbul University Cardiology Institute, Istanbul, Turkey; [2]Department of Cardiology, University of Health Sciences, Hamidiye Faculty of Medicine, Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital, Istanbul, Turkey; [3]Department of Pediatric Cardiology, Hacettepe University Hospitals, Hacettepe University Hospitals, Ankara, Turkey; [4]Department of Pediatric Cardiology, Gazi University Hospital, Ankara, Turkey; [5]Department of Pediatric Cardiovascular Surgery, Koc University Hospital, Istanbul, Turkey; [6]Department of Pediatric Cardiology, Koc University Hospital, Istanbul, Turkey; [7]Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, USA; [8]Department of Cardiology, Hacettepe University Hospitals, Ankara, Turkey; [9]Actelion Pharmaceuticals Ltd, Istanbul, Turkey

Abstract

Pulmonary hypertension is a group of diseases, including pulmonary arterial hypertension associated with congenital heart disease (APAH-CHD), characterized by progressive deterioration in pulmonary hemodynamics associated with substantial morbidity and mortality risk. THALES is a national multicenter, prospective observational registry, providing data on patients with APAH-CHD. The study comprised APAH-CHD patients (>3 months of age) with confirmed diagnosis of right heart catheterization or echocardiographic findings. Initial and follow-up data were collected via regular hospital visits. Descriptive statistics are used for definitive purposes. Overall, 1034 patients aged 3 months–79 years (median 11.2 [Q1–Q3: 2.2–24.3] years) with APAH-CHD were enrolled at 61 centers, 50.3% being retrospectively enrolled. Most had either Eisenmenger's syndrome (49.2%) or systemic-to-pulmonary shunts (42.7%). Patients were mostly in functional class I–II at the time of diagnosis (46.6%). Mean 6-min walk distance (6MWD) was 369 ± 120 m. Mean pulmonary arterial pressure was 54.7 ± 22.2 mmHg for the whole group, and was highest in patients with Eisenmenger's syndrome. Targeted therapies were noted in 398 (38.5%) patients (monotherapy in 80.4%). Follow-up data were available in 506 patients. Survival at 140 months was 79% and was associated with baseline 6MWD >440 m ($p = 0.009$), brain natriuretic peptide level < 300 ng/L ($p < 0.001$). Follow-up 6MWD >165 m ($p < 0.0001$), brain natriuretic peptide level <300 ng/L ($p = 0.031$), and targeted therapies ($p = 0.004$) were also predictive of survival. THALES is the largest registry dedicated to APAH-CHD to date and provides important contributions on demographics, clinical characteristics, and gaps in disease management.

Keywords

pulmonary arterial hypertension, pulmonary arterial hypertension associated with congenital heart disease, registry, Eisenmenger's syndrome, THALES

Date received: 27 October 2020; accepted: 23 May 2021

Pulmonary Circulation 2021; 11(3) 1–10
DOI: 10.1177/20458940211024206

Pulmonary hypertension (PH) is defined as a group of diseases characterized by progressive deterioration in pulmonary hemodynamics leading to right ventricular failure and decreased functional capacity, often associated with substantial morbidity and mortality risk.[1] Pulmonary arterial

Corresponding author:
Serdar M. Kücükoglu, Department of Cardiology, Istanbul University Cardiology Institute, Haseki Caddesi, Istanbul 34096, Turkey.
Email: kucukoglu3@yahoo.com

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hypertension (PAH) is the first of five groups of PH in current clinical classification of this disease[2,3] and includes different forms of precapillary PH sharing a similar clinical picture and identical histopathological changes of pulmonary microcirculation. PAH associated with congenital heart diseases (APAH-CHD) has become one of the most important types of PAH,[3] and has been classified into four clinical subgroups: Eisenmenger's syndrome (subgroup I); PAH associated with prevalent systemic-to-pulmonary shunts (subgroup II); PAH with small or coincidental defects (subgroup III); and PAH that either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative hemodynamic lesions (subgroup IV).[3]

Recent improvements in congenital heart disease (CHD) management have enabled more pediatric patients with complex and/or repaired CHD to survive until adulthood, with increased disease complexity. The changing face of APAH-CHD has been described in large registries and reviews.[4–9] Approximately 6–10% of adults with CHD have been reported to develop PAH.[4–9]

Although recommendations for treatment of Eisenmenger's syndrome and correctability criteria for prevalent systemic-to-pulmonary shunts have been clarified, management strategies in the other subgroups remain to be determined.[3] Moreover, the vast majority of the APAH-CHD data have been derived from series representing a western population, so differential patterns of disease progression in the rest of the world need to be evaluated.[6–10]

The **T**urkish Congenital **H**eart Disease – **A**ssociated Pu**l**monary Arterial Hyp**e**rtension **S**tudy (THALES) has been designed to evaluate demographic and clinical characteristics, laboratory, echocardiographic and hemodynamic findings, treatment patterns, and outcomes in pediatric and adult patients with APAH-CHD.

Methods

THALES is a nationwide, multicenter, observational registry conducted in 61 centers across Turkey, either within university-affiliated medical centers, teaching and research hospitals, or community hospitals. The registry was designed and supervised by the steering committee (the steering committee consists of the manuscript authors).

Study population

The study comprised APAH-CHD patients (>3 months of age) in whom diagnosis was confirmed by right heart catheterization as the presence of mean pulmonary arterial pressure (mPAP) >25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) >3 Wood units. If right heart catheterization could not be performed for reasons such as patient refusal or lack of documentation, echocardiographic (echo) findings were adopted for confirmation of PAH by consideration of the steering committee. The diagnostic criteria and classification were set based on 2009 European Society of Cardiology (ESC) and European Respiratory Society (ERS) PH guidelines available at the time of study design.[11]

Data collection

Demographic data and patient characteristics including age at diagnosis and enrollment, gender, APAH-CHD classification, medical and family history, presenting symptoms, 6-min walk distance (6MWD), functional class (FC), echo, hemodynamic indices of pulmonary circulation, and left and right ventricle systolic function were documented with an electronic case record form. The patients who had undergone right heart catheterization, or if not available echocardiography, within three months before enrollment were considered as prospective patients. Retrospective enrollment was allowed for up to two-thirds of the total patients to shorten the recruitment period. For retrospectively recorded patients, data collected at time of diagnosis, significant clinical event occurrence, or latest available visit were recorded. For the first cross-sectional analysis, the cut-off date for data inclusion was September 2011, when the number of patients enrolled exceeded the planned number of 1000. For functional classification, Ross[12] and World Health Organization[13] definitions were used for patients aged <3 years and >3 years, respectively.

Baseline echo and right heart catheterization measurements were to be within one week of diagnosis to confirm patients' situations at time of diagnosis. The investigators were expected to measure, calculate, and record systolic, diastolic, and mean pulmonary arterial pressures (sPAP, dPAP, and mPAP), transpulmonary and transsystemic pressure gradients, the ratios of pulmonary flow to systemic flow (Qp/Qs), and PVR to systemic vascular resistance (SVR). Pulmonary and systemic blood flow were calculated with the Fick method for patients with unrepaired or partially repaired lesions, whereas either the Fick or thermodilution methods were used for patients with repaired lesions or small defects concomitant with PAH.[14]

The steering committee evaluated each case with inconsistent data based on the PVR measures, PVR/SVR ratio, and other clinical and HD parameters to confirm Eisenmenger's syndrome diagnosis and resolve data inconsistency.

Data management and analyses were performed by a contract research organization. All prospective patients meeting enrollment criteria were informed of the study protocol and provided written consent for use of their health data. Parental consent was obtained for patients aged < 18 years.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA).

Descriptive statistics were used for definitive purposes, including frequencies and percentages of nonmissing values for categorical data and mean ± standard deviation or median (1st–3rd quartile values) for continuous variables. Comparisons between subgroups were performed by using the Kruskal–Wallis Test, Mann–Whitney U test, Student's-*t* test, Pearson Chi-square, or Fisher's exact test, as appropriate. The two-sample *t* test was used when the data were approximately distributed normally, and the two-sample Mann–Whitney U test was used for variables not normally distributed. The correlation coefficients and their significances were calculated using the Spearman test. A 5% type-I error level was used for statistical significance. The Kaplan–Meier estimates and Breslow Chi-square tests were used for survival analysis and intergroup differences, respectively. The time of initiation of monotherapy and combination therapy was taken as time 0 in the survival analysis.

Results

According to the protocol, 1034 patients (male 434, female 600) aged between 3 months and 79 years were enrolled from May 2009 through September 2011. Of those, 30 (2.9%) were included according to echo findings consistent with APAH-CHD. Retrospectively enrolled patients accounted for 50.3% ($n = 509$) of the cohort.

Clinical and anatomical-pathophysiological characteristics of patients

Baseline clinical characteristics are summarized in Table 1. Median (Q1–Q3) patient ages at diagnosis and enrollment were 8.7 (1.4–23.4) years and 11.2 (2.2–24.3) years, respectively. Thirty-five percent of patients were aged >18 years. Clinical classification was not documented in 43 patients, and an additional 12 patients had complex congenital cyanotic heart disease; these 55 patients were not included in baseline analysis. Eisenmenger's syndrome was diagnosed in 49.2% of patients, while subgroups II, III, and IV constituted 42.7%, 1.1%, and 7.0% of the remaining 979 patients, respectively. Baseline demographic, clinical, hemodynamic, and treatment characteristics of the study patients are summarized in Table 1. Ventricular septal defects (VSD) were the most frequent lesion followed by atrial septal defects (ASD), patent ductus arteriosus (PDA), and atrioventricular septal defects (AVSD) (Supplementary Fig. S1). The most frequent lesion was VSD in subgroups I (Eisenmenger's syndrome), II, and IV, whereas ASD was the most frequent in subgroup III (Table 1).

Dyspnea was the most frequent symptom at diagnosis, followed by cyanosis, chest pain, hemoptysis, and syncope/pre-syncope, which was most frequently reported in subgroup IV and in patients < 6 years of age (Table 1, Supplementary Fig. S2).

Functional assessment

Functional classification could be performed for 742 patients. The vast majority of patients were in FC I–II at the time of diagnosis (46.6%). While most patients were in FC III–IV in subgroup I (Eisenmenger's syndrome, 35.9%), most patients in subgroups II, III, and IV were in FC I–II (63.4%, 45.53%, and 47.1%, respectively; Table 1). Patients aged <3 years were mostly in FC II (76%), while patients >3 years were equally distributed between FC II and III (49% and 42%, respectively; data not shown). 6MWD was reported in 314 (30.4%) out of 1034 patients and the mean 6MWD was 369 ± 120 m which was comparable among the subgroups ($p = 0.095$; Table 1). 6MWD was recorded in 61 (19.4%) patients aged <10 years, 101 (32.2%) patients aged 11–18 years, and 152 (48.4%) patients aged >18 years. Patients in FC I and II had longer 6MWD (457 ± 29 m and 462 ± 95 m, respectively) compared to the patients in FC III (324 ± 84 m) and IV (64 ± 25 m) ($p < 0.001$; data not shown).

Hemodynamic findings

Hemodynamic measures of the overall cohort and clinical subgroups are demonstrated in Table 1. Overall mean mPAP was 54.7 ± 22.2 mmHg and significantly higher in subgroup I (Eisenmenger's syndrome) compared to the subgroups II, III, and IV ($p < 0.001$). Subgroup II had the lowest PVR and PVR/SVR ratio compared to other subgroups ($p < 0.001$; Table 1). Vasoreactivity test was reported for 863 (83.5%) patients and 68.5% of these were < 18 years old. Positive response was noted in 12.5% and 7.0% of pediatric and adult patients, respectively (data not shown).

The PVR/SVR, mPAP/mSAP, and sPAP/sSAP ratios correlated with FC ($p < 0.001$), but not with 6MWD ($p = 0.099$; Supplementary Figs. S3 and S4).

Pre- and post-tricuspid defects were recorded in 197 (19%) and 837 (81%) patients, respectively. Patients with post-tricuspid defects were younger at diagnosis (13 ± 14 vs. 35 ± 21 years; $p < 0.0001$), whereas gender and 6MWD were comparable. Mean values of sPAP (87 ± 28 vs. 71 ± 30 mmHg; $p < 0.0001$), mPAP (56 ± 22 vs. 46 ± 22 mmHg; $p < 0.0001$), and PVR/SVR ratio (0.41 ± 0.51 vs. 0.28 ± 0.27; $p < 0.01$) were higher in patients with post- versus pre-tricuspid defects, while Qp/Qs ratios were similar (data not shown).

PAH-targeted therapy patterns

Clinical and hemodynamic characteristics of patients treated with targeted therapy (TT) are summarized in Supplementary Table S1. TT was noted in 40.1% of the overall population. Among the 415 patients treated with TT, monotherapy was the treatment of choice in 80.7%. Treated patients were significantly older and had higher mean mPAP, mSAP, PVR/SVR, and PVR values. Ventricular septal defect, PDA, or AVSD patients were

Table 1. Baseline demographic, clinical, hemodynamic, and treatment characteristics of the study patients.

Variable	All ($n=1034$[a])	Subgroup I ($n=482$)	Subgroup II ($n=418$)	Subgroup III ($n=11$)	Subgroup IV ($n=68$)	*p*-value
Age, year						
Age at diagnosis, years, median (Q1–Q3)	8.7 (1.4–23.4)	10.7 (2.8–19.1)	4.0 (0.7–26.7)	4.8 (2.8–40.9)	24.7 (9.3–40.6)	<0.001
Age at enrollment, years, median (Q1–Q3)	11.2 (2.2–24.3)	13.4 (4.9–21.3)	5.7 (1.1–27.1)	5.8 (4.4–44.6)	26.4 (12.8–43.1)	<0.001
Time from diagnosis to enrollment, months, median (Q1–Q3)	3.4 (0.1–20.6)	8.4 (0.2–34.5)	0.4 (0.0–10.0)	14.4 (0.5–41.9)	5.5 (0.1–13.7)	<0.001
Sex, *n* (%)						NS
Female	600 (58.0)	286 (58.7)	237 (56.0)	4 (36.4)	48 (69.1)	
Male	434 (42.0)	202 (41.3)	186 (44.0)	7 (63.6)	21 (30.9)	
Enrollment status ($n=1011$[b]), *n* (%)						<0.001
Newly diagnosed	502 (49.7)	187 (38.8)	261 (62.4)	4 (36.4)	28 (43.1)	
Retrospectively recorded	509 (50.3)	295 (61.2)	157 (37.6)	7 (63.6)	37 (56.9)	
Not known		6	5	–	4	
FC ($n=742$[c]), *n* (%)						
FC I–II	482 (46.6)	157 (32.6)	265 (63.4)	5 (45.53)	32 (47.1)	§
FC III–IV	260 (25.1)	173 (35.9)	71 (17.0)	1 (9.17)	9 (13.2)	§
Missing data	292 (28.9)	152 (31.5)	82 (19.6)	5 (45.3)	27 (39.7)	
6MWD[d], m, ($n=314$), mean ± SD	369 ± 120	368 ± 119	340 ± 134	416 ± 87	403 ± 100	0.095
Specific treatment, (yes/no), *n* (%)	398 (38.5)	291 (60.4)	80 (19.1)	4 (36.4)	23 (33.8)	<0.000
Monotherapy	320 (31.0)	237 (49.2)	60 (14.4)	4 (36.4)	19 (27.9)	
Combination therapy	78 (7.5)	54 (11.2)	20 (4.8)	0	4 (5.9)	
Hemodynamic characteristics, mean ± SD						
PVR, WU.m^2	8.77 ± 6.84	12.20 ± 7.1	4.21 ± 1.28	11.09 ± 10.11	10.95 ± 8.88	<0.001
SVR, WU.m^2	19.92 ± 9.98	19.17 ± 8.41	20.58 ± 11.56	27.53 ± 17.55	22.94 ± 12.55	NS
PVR/SVR, WU.m^2	0.62 ± 0.50	0.85 ± 0.46	0.26 ± 0.13	0.44 ± 0.09	0.88 ± 0.96	<0.001
mPAP, mmHg	54.7 ± 22.2	69.2 ± 18.3	39.1 ± 13.9	54.3 ± 21.2	51.3 ± 22.2	<0.001
sPAP, mmHg	84.6 ± 29.4	103.0 ± 23.1	64.4 ± 20.8	84.8 ± 29.1	78.9 ± 31.4	<0.001
mSAP, mmHg	77.3 ± 16.9	78.9 ± 16.2	75.9 ± 17.2	68.7 ± 20.9	79.8 ± 17.1	0.026
sSAP, mmHg	103.7 ± 22.5	104.7 ± 21.5	102.9 ± 22.8	98.3 ± 21.3	106.9 ± 21.7	NS
mPAP/mSAP, mmHg	0.74 ± 0.33	0.89 ± 0.32	0.55 ± 0.23	0.75 ± 0.19	0.67 ± 0.30	<0.001
sPAP/sSAP, mmHg	0.83 ± 0.26	0.99 ± 0.15	0.65 ± 0.24	0.83 ± 0.22	0.75 ± 0.30	<0.001
Qpi, L/min/m^2	5.43 ± 2.87	4.9 ± 2.56	6.36 ± 3.04	3.59 ± 1.79	4.86 ± 3.01	<0.001
Qsi, L/min/m^2	3.29 ± 1.75	3.59 ± 1.82	2.97 ± 1.55	1.32 ± 0.24	3.29 ± 1.85	0.001
Qp/Qs	1.89 ± 1.20	1.13 ± 0.26	2.77 ± 1.29	1.79 ± 1.40	1.89 ± 0.89	<0.001
SVO_2, %	65.6 ± 11.3	65.5 ± 11.9	65.7 ± 10.7	69.7 ± 9.8	67.6 ± 9.4	NS
SAO_2, %	91.4 ± 7.6	85.5 ± 6.2	95.5 ± 3.9	91.5 ± 6.9	93.8 ± 5.4	<0.001
Defects, *n* (%)	1132	562	499	13	58	
ASD	300 (26.5)	99 (33)	172 (57.3)	6 (2.0)	23 (7.6)	
VSD	532 (47)	288 (54.1	215 (40.4)	5 (0.9)	24 (4.5)	
PDA	170 (15)	101 (59.4)	61 (35.9)	1 (0.6)	7 (4.1)	
AVSD	130 (11.5)	74 (56.9)	51 (39.2)	1 (0.8)	4 (3.1)	
Symptoms, *n* (%)						
Dyspnea	917 (92)	437 (89.6)	389 (91.9)	9 (81.8)	52 (75.0)	#
Cyanosis	536 (54)	479 (98.1)	41 (9.6)	3 (27.3)	10 (14.7)	<0.001
Chest pain	108 (11)	62 (12.7)	42 (9.8)	–	3 (4.4)	**
Syncope–pre-syncope	62 (6.0)	35 (7.1)	16 (3.8)	–	11 (16.2)	††
Hemoptysis	72 (7.0)	25 (5.2)	38 (9.1)	1 (9.1)	2 (2.9)	‡‡

6MWD: 6-min walk distance; ASD: atrial septal defects; AVSD: atrioventricular septal defects; FC: functional class; mPAP: mean pulmonary arterial pressure; mSAP: mean systemic arterial pressure; NS: not significant; PDA: patent ductus arteriosus; PVR: pulmonary vascular resistance; Q1-Q3: 1st–3rd quartile; SD: standard deviation; sPAP: systolic pulmonary arterial pressure; sSAP: systolic systemic arterial pressure; SVR: systemic vascular resistance; VSD: ventricular septal defects; WU: wood unit.

Note: Subgroup I: Eisenmenger's syndrome; subgroup II: pulmonary arterial hypertension associated with prevalent systemic-to-pulmonary shunts; subgroup III: small defects; subgroup IV: post-correction residual pulmonary arterial hypertension.

[a]Clinical classification was not available in 43 patients and 12 patients had complex congenital cyanotic heart disease; these 55 patients were not included in baseline analysis.

[b]Enrollment status was not available in 23 patients.

[c]Functional class was not available in 292 patients.

[d]6-min walk distance is noted only for 314 patients.

§ >3 cells have expected count less than 5.

Two cells (20.0%) have expected count less than 5. The minimum expected count is 0.93.

** Two cells (20.0%) have expected count less than 5. The minimum expected count is 1.20.

†† Three cells (30.0%) have expected count less than 5. The minimum expected count is 0.70.

‡‡ Three cells (30.0%) have expected count less than 5. The minimum expected count is 0.76.

more likely to be treated compared with ASD patients ($p < 0.001$). Bosentan was the most frequently used drug as monotherapy (78%), followed by inhalation iloprost (18%) and sildenafil (4%). The most preferred combination was bosentan plus iloprost (54%), followed by bosentan plus sildenafil (33%; Supplementary Fig. S5). The highest rate of combination therapy was documented in the subgroup I (Eisenmenger's syndrome), followed by the subgroups IV and II, while no combination therapy was noted in subgroup III (Table 1). Two-thirds of patients in FC III–IV were treated with TT, while treatment rate was only 21.6% for the patients in FC I–II.

Long-term follow-up

Follow-up data were available for 506/1034 patients enrolled (Table 2). The median age of patients with follow-up was 13.6 years and median follow-up from diagnosis was 39 months (data not shown). Patients with follow-up data comprised 237 patients in the subgroup I (Eisenmenger's syndrome), 223 in the subgroup II, 9 in the subgroup III, and 37 in the subgroup IV. These patients were older and had a higher baseline risk profile, as indicated by significantly worse FC and hemodynamic measures compared to patients without follow-up data (Table 2). Seventy-nine percent of the patients who were followed up ($n = 506$) were alive at 140 months. Having 6MWD over 440 m ($p = 0.009$) at baseline and 6MWD above 165 m at follow-up ($p < 0.0001$; Fig. 1), brain natriuretic peptide levels < 300 pg/mL at baseline ($p < 0.001$; Fig. 2) and follow-up ($p = 0.031$), and TT ($p = 0.004$; Supplementary Fig. S6), regardless of monotherapy or combination, were significantly associated with better survival. Clinical and anatomical-pathopyhsiological groups, baseline cardiac index, and PVR were not associated with any survival differences (Supplementary Figs. S7 to S11).

Discussion

Improvements in CHD surgery for the last four decades have resulted in improved survival even in patients with complex defects, increasing the number of patients surviving to adulthood. Due to improved longevity in this population at childhood, prevalence of CHD increased from 0.5% to 5.1–5.2% between 2000 and 2012/2013 in European countries, and is estimated to be 11% by 2030.[15,16] The

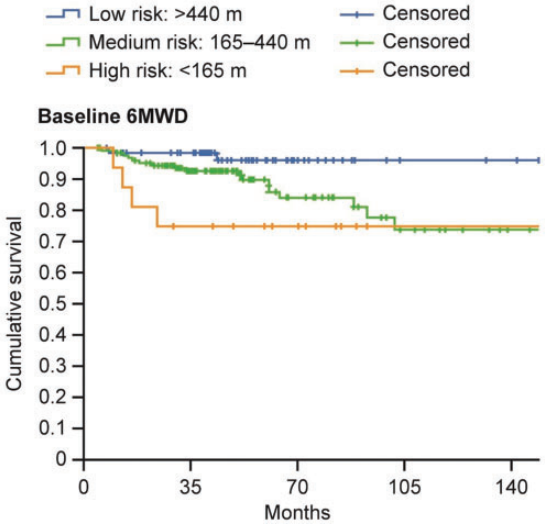


Fig. 1. Survival according to follow-up 6-min walk distance.

Table 2. Hemodynamic and clinical characteristics in patients with pulmonary arterial hypertension associated with congenital heart disease according to follow-up status.

Variable	All ($n = 1034$)	Without follow-up ($n = 521$)	With follow-up ($n = 506$)	*p*-value
Sex, *n* (%)				0.543
Male	434 (42.0)	227 (52.3)	207 (47.7)	
Female	600 (58.0)	301 (50.2)	299 (49.8)	
FC, *n* (%)	742 (71.8)	378 (50.9)	364 (49.1)	0.001
FC I–II	482 (65.0)	267 (21.6)	215 (78.4)	
FC III–IV	260 (35.0)	111 (42.7)	149 (57.3)	
CHD subgroup, *n* (%)	1034 (100.0)	528	506	0.117
I	509 (49.2)	272 (53.4)	237 (46.6)	
II	441 (42.6)	218 (49.4)	223 (50.6)	
III	12 (1.2)	3 (25.0)	9 (75.0)	
IV	72 (7.0)	35 (48.6)	37 (51.4)	
Hemodynamic parameters				
mPAP, mmHg, mean ± SD		52.32 ± 21.96	57.11 ± 22.1	0.001
mRAP, mmHg, mean ± SD		9.05 ± 3.35	8.85 ± 2.83	0.839
PVR, WU, mean ± SD		8.05 ± 6.11	9.55 ± 7.49	0.018
Qpi/Qsi, mean ± SD		1.97 ± 1.25	1.8 ± 1.15	0.008

ASD: atrial septal defects; AVSD: atrioventricular septal defects; CHD: congenital heart diseases; FC: functional class; mPAP: mean pulmonary arterial pressure; mSAP: mean systemic arterial pressure; PVR: pulmonary vascular resistance; SD: standard deviation; VSD: ventricular septal defects; WU: wood unit.

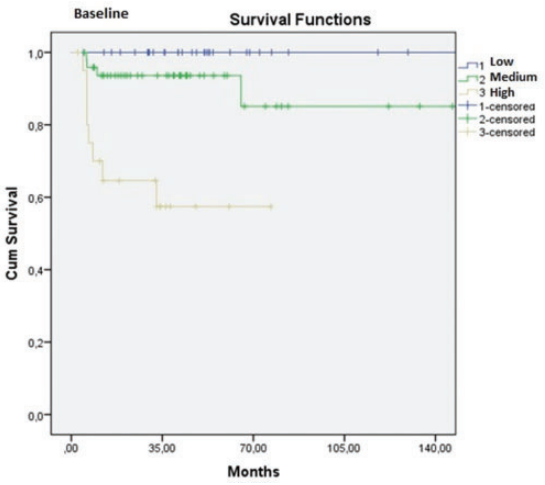


Fig. 2. Survival according to baseline brain natriuretic peptide level.

CONCOR registry showed that PAH prevalence was 3.2% in the overall adult CHD population in the Netherlands, increasing with age from 2.5% to 10% and 35% in patients <30 years, 30–60 years, and >60 years, respectively.[17]

APAH-CHD is an important clinical problem in Turkey, as survey data from SIMURG (nationwide adult PH registry) documented that APAH-CHD accounted for 47% of the adult PAH population in Turkey.[18]

The THALES registry evaluated demographic, clinical, and hemodynamic characteristics, TT patterns, and outcomes across different clinical and anatomical-pathophysiological APAH-CHD subgroups. Moreover, multiple comparisons among the clinical, age, and pre- versus post-tricuspid defect subsets were performed.

In the THALES registry, most patients were diagnosed as Eisenmenger's syndrome or PAH with prevalent left-to-right shunts (49.2% and 42.7, respectively). This registry has similar rates of patients with Eisenmenger's syndrome as Bologna data (49.2 vs. 47%, respectively),[19] while CONCOR has fewer patients Eisenmenger's syndrome (38%).[17] This difference may be due to a decline in the number of patients with Eisenmenger's syndrome in Europe, as shown in a retrospective population-based study investigating temporal changes in incidence, prevalence, and mortality in patients with Eisenmenger's syndrome. The 35-year study was conducted in the Nordic region and revealed a decrease in Eisenmenger's syndrome incidence from 2.5 to 0.2/million inhabitants/year and in prevalence from 24.6 to 11.9/million inhabitants.[20] The prevalence of patients in subgroup IV in the THALES registry (7%) was lower than either the CONCOR registry or the Bologna data (47.4% and 23%, respectively).[17,19] A higher rate of inoperable patients due to late diagnosis may explain this difference.

The THALES data confirm a female predominance in patients with APAH-CHD regardless of age, consistent with other registries.[6–9] Median (Q1–Q3) age of patients at diagnosis was 8.7 years (1.4–23.4) in the overall APAH-CHD population, 10.7 years (2.8–19.1) in subgroup I (Eisenmenger's syndrome), and 4.0 years (0.7–26.7) in subgroup II. Although the difference in median age suggests progression from a clinical status of PAH with prevalent left-to-right shunt to subgroup I (Eisenmenger's syndrome) is a continuum, there may be other mechanisms of this progression that remain to be determined.

Symptoms in the study population were similar to those reported in the literature, dyspnea being the most frequent, followed by cyanosis. Syncope was more prevalent in subgroup IV compared with subgroups I and II, and not recorded in subgroup III. This may be due to the presence of concomitant small VSD or ASD with severe pulmonary vascular disease, similar to those in idiopathic pulmonary hypertension. These small defects might contribute to the compensation of the right-sided pressure overload by shunting to the systemic circulation. A history of syncope was most frequently recorded in patients aged 18–35 years (17%). While events noted for children were lower than those reported in the TOPP registry (3.5% vs. 25%),[6] syncope rates in adults were comparable to other adult registries.[6–20] Low incidence of syncope in THALES may relate to the absence of idiopathic pulmonary hypertension and heritable PAH in the study population.

Although 6MWD has been the most utilized measure in assessing treatment effect of TT for PAH, the predictive value of this test has been questioned recently because of limitations such as lack of standardization in relation to demographic characteristics and comorbidities, and difficulties in its interpretation at early childhood.[21,22] Among the overall CHD population, patients with Eisenmenger's syndrome reportedly have the most severely limited exercise capacity. In THALES, 6MWD was reported in 50% of adult patients and 20% of those aged < 18 years. Frequency of 6MWD use in the study cohort was lower than reported in TOPP and REVEAL.[6,9] This is assumed to be partially due to lack of appropriate healthcare documentation despite the test being performed, and retrospective patient enrollment.

Although a vasoreactivity test has not been indicated in subgroups other than idiopathic pulmonary hypertension, heritable, or drug-associated PAH,[3] in THALES, a vasoreactivity test was documented in 83.5% patients. This was due to both the requirement for vasoreactivity test as part of the correctability assessment in pediatric patients, and vasoreactivity being a prerequisite for reimbursement of TT prescriptions in Turkey. The vasoreactivity rate in the THALES pediatric and adult populations was in concordance with published studies.[23–26]

The THALES study showed no difference in survival in terms of clinical and anatomical-pathophysiological classifications of APAH-CHD in accordance with results of the REVEAL APAH-CHD cohort.[9] However, according to Bologna data, patients in subgroup I (Eisenmenger's

syndrome) or subgroup II had better survival compared to patients with PAH with small/coincidental defects (subgroup III) or PAH after defect repair (subgroup IV).[19] Improved survival in Eisenmenger's syndrome has been attributed to the preservation of right ventricle function as a result of earlier myocardial remodeling with persistent hypertrophy and maintenance of the cardiac output through the reversed shunt at the expense of systemic desaturation.

In the updated risk algorithm from the 2015 ESC/ERS PH guidelines, based on estimated annual PAH mortality risk, 6MWD >440 m and/or brain natriuretic peptide < 50 ng/L are consistent with low risk, while 6MWD < 165 m and/or brain natriuretic peptide >300 ng/L are associated with high-risk status.[3] However, it has been pointed out that "most of those variables have been validated mostly for idiopathic pulmonary hypertension and the cut-off levels used above may not necessarily apply to other forms of PAH".[3] In THALES, consistent with the risk-based treatment algorithm of PAH recommended by the ESC/ERS guidelines, 6MWD >440 m at baseline and 6MWD >165 m at follow-up, and brain natriuretic peptide level < 300 pg/mL at both baseline and follow-up were found to discriminate survival curves in the APAH-CHD population.

Dimopoulos et al.[27] reported that FC I–II versus III–IV was associated with better seven-year outcomes in patients with Eisenmenger's syndrome. Moreover, a French multicenter Eisenmenger's syndrome study reported that World Health Organization FC III/IV, lower peripheral arterial O_2 saturation percentage, and pre-tricuspid defects were predictors of events.[28] In contrast to other studies, FC and hemodynamic measures such as PVR/SVR, mPAP/mSAP, and sPAP/sSAP ratios, which correlated with FC, were not found to be predictive for survival in THALES. This may be due to the fact that other studies enrolled only patients with Eisenmenger's syndrome and this study enrolled higher number of FC II patients.

The THALES registry provides important insights into the current treatment of patients with APAH-CHD. PAH-specific treatment was noted in 40.1% of the study group. Subgroup I had the highest rate of TT: 60.4%, 19.1%, 36.4%, and 33.8% for subgroups I, II, III, and IV, respectively. Monotherapy was the most frequently used treatment in both children and adult patients (Table 1). Although hemodynamic measures were better in the untreated group, survival was improved in the treated group because of the treatments given; however, the effect of treatments could not provide a significant survival difference between the two groups. Bosentan was the first treatment of choice, followed by inhaled iloprost and sildenafil in the overall registry population. Combination therapy was more frequently preferred in the Eisenmenger's syndrome subset, and in patients at FC III and IV. Bosentan and inhaled iloprost were the most commonly used combination, followed by bosentan and sildenafil. Treatment patterns in THALES are in accordance with the ESC grown-up congenital heart disease and new ESC/ERS PH guidelines recommendations for PAH TT, which have focused on patients with Eisenmenger's syndrome.[3,29] Bosentan is recommended in FC III patients with Eisenmenger's syndrome (class IB), while other endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors, and prostanoids should be considered (class IIaC), and combination therapy may be considered in patients with Eisenmenger's syndrome (class IIbC).[3] Although the ESC/ERS PH guidelines have provided no specific recommendation for a PAH TT algorithm in the other three subgroups of APAH-CHD, the American Heart Association scientific statement, in its more liberal recommendation, stated, "treatment of adult congenital heart disease with PAH with pulmonary arterial vasodilator drugs, in appropriate settings, can be useful and can lead to functional improvement in many diagnoses (class IIa, B)".[3,23] It seems we have followed the American Heart Association scientific statement in treating subgroup II, III, and IV patients with TT.

In the study cohort, patients treated with TT had worse clinical and hemodynamic features, as expected. Only approximately 1/5 of FC I–II patients were treated with PAH TT, while 2/3 FC III–IV patients were treated with PAH TT. Consistent with results of other APAH-CHD series, the follow-up cohort revealed that, regardless of mono- or combination therapies, TT versus no TT was associated with significantly better survival.[27,28,30]

Limitations

Presented data were mainly based on cross-sectional evaluation of baseline clinical, hemodynamic, and TT characteristics in patients with APAH-CHD, and follow-up data were provided from almost half the enrolled patients. Being observational, partially retrospective, and multicentric might cause some data heterogeneity. An important difficulty we encountered is that recording and archiving medical information was found to be insufficient in many hospitals, evidenced by difficulties reaching retrospective patient records or analyzing non-standardized heterogeneous retrospective data. However, as a result of the inclusion criteria, definitive hemodynamic data were available for most patients.

The high rate of missing data both at baseline and follow-up was a limitation of this partially retrospective study. Additionally, as a general trend, there is a flow of cases from small centers to large centers in our country. The amount of missing data was limited in the experienced major centers, although the cumulative effect of missing data is significant. Moreover, some of the patients in the subgroup II may have undergone percutaneous or surgical closure with physician discretion and may have joined the missing data pool, and temporal tracking of these patients

was not within the scope of this study, which might be considered another limitation. Finally, retrospective inclusion of patients in this study looking at survival carries the risk of an immortal time bias.

Conclusion

THALES is the largest, nationwide multicenter registry representing real-life practice in terms of demographics, diagnostic algorithms, risk stratifications, and PAH TT patterns and outcomes across clinical and anatomical-pathophysiological subgroups of APAH-CHD, providing important information on top of available data. The 6MWD and brain natriuretic peptide level at baseline and follow-up, and TT, but not clinical and anatomical-pathophysiological classifications of APAH-CHD and baseline hemodynamic measures of pulmonary circulation, were found to be associated with survival in the study population.

Acknowledgements

THALES Registry Investigators: Abdurrahman Oğuzhan from Erciyes University Medical Faculty, Kayseri, Turkey; **Abdurrahman Üner** from Yüzüncü Yıl University Medical Faculty, Van, Turkey; **Alp Aydınalp** from Başkent University Medical Faculty, Ankara, Turkey; **Alperen Aydın** from Osmangazi University Medical Faculty, Eskişehir, Turkey; **Arda Saygılı** from Acıbadem Bakırköy Hospital, Istanbul, Turkey; **Aygün Dindar** from Istanbul University Istanbul Medical Faculty, Istanbul, Turkey; **Ayşe G. Eroğlu** from University Cerrahpaşa Medical Faculty, Istanbul, Turkey; **Ayşe Yıldırım** from Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, Istanbul, Turkey; **Bahadır Kırılmaz** from Çanakkale Onsekiz Mart University Medical Faculty, Çanakkale, Turkey; **Bahri Akdeniz** from Dokuz Eylül University Medical Faculty, Izmir, Turkey; **Birgül Varan** from Başkent University Medical Faculty, Ankara, Turkey; **Burçak Kılıçkıran** from Başkent University Medical Faculty, Adana, Turkey; **Bülent B. Altunkeser** from Selçuk University Medical Faculty, Konya, Turkey; **Bülent Mutlu** from Marmara University Medical Faculty, Istanbul, Turkey; **Cemşid Karakurt** from Inönü University Medical Faculty, Malatya, Turkey; **Cihan Örem** from Karadeniz Technical University Medical Faculty, Trabzon, Turkey; **Dolunay Gürses** from Pamukkale University Medical Faculty, Denizli, Turkey; **Ender Ödemiş** from Istanbul Mehmet Akif Ersoy Training and Research Hospital, Istanbul, Turkey; **Ercan Tutar** from Ankara University Medical Faculty, Ankara, Turkey; **Ertürk Levent** from Ege University Medical Faculty, Izmir, Turkey; **Figen Akalın** from Marmara University Medical Faculty, Istanbul, Turkey; **Fuat Gündoğdu** from Atatürk University Medical Faculty, Erzurum, Turkey; **Gül Sagın Saylam** from Dokuz Eylül University Medical Faculty, Izmir, Turkey; **Halil Ertuğ** from Akdeniz University Medical Faculty, Antalya, Turkey; **Kemal Baysal** from Ondokuz Mayıs University Medical Faculty, Samsun, Turkey; **Mehmet Eren** from Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey, **Mehmet Uzun** from Sultan Abdülhamid Han Research and Training Hospital, Istanbul, Turkey, **Mehmet Yokuşoğlu** from Gülhane Training and Research Hospital, Ankara, Turkey; **Meral Kayıkçıoğlu** from Ege University Medical Faculty, Izmir, Turkey; **Meryem Aktoz** from Trakya University Medical Faculty, Edirne, Turkey; **Murat Çaylı** from Adana Numune Training and Research Hospital, Adana, Turkey; **Mustafa O. Bulut** from Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey, **Naci Ceviz** from Atatürk University Medical Faculty, Erzurum, Turkey; **Nazmi Narin** from Erciyes University Medical Faculty, Kayseri, Turkey; **Olgu Hallıoğlu** from Mersin University Medical Faculty, Mersin, Turkey; **Orhan Özer** and **Osman Başpınar** from Gaziantep University Medical Faculty, Gaziantep, Turkey; **Özlem Bostan** from Uludağ University Medical Faculty, Bursa, Turkey; **Recep Demirbağ** from Harran University Medical Faculty, Şanlıurfa, Turkey; **Sanem Nalbantgil** from Ege University Medical Faculty, Izmir, Turkey; **Selmin Karademir** from Dr. Sami Ulus Gynecology and Pediatrics Training and Research Hospital, Ankara, Turkey; **Sevcan Erdem** from Çukurova University Medical Faculty, Adana, Turkey; **Sümeyye Güllülü** from Uludağ University Medical Faculty, Bursa, Turkey; Timur Meşe from Izmir Behçet Uz Pediatric Diseases and Surgery Training and Reasearch Hospital, Izmir, Turkey; and Türkay Özcan from Mersin University Medical Faculty, Mersin, Turkey.

Conflict of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MSK has received consultancy fees from and served as an advisory board member for Actelion Pharmaceuticals Ltd, Bayer, GSK, and Abdi Ibrahim; has received speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GSK, Pfizer, Abdi Ibrahim, and Sandoz; has been a clinical trial investigator for Actelion Pharmaceuticals Ltd, Bayer, Novartis, and Pfizer; has received congress sponsorship from Actelion Pharmaceuticals Ltd, Bayer, Pfizer, Abdi Ibrahim, and Dem Pharmaceuticals; and has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. CK has received consultancy fees from and served as an advisory board member for Actelion Pharmaceuticals Ltd, Bayer, and Dem Pharmaceuticals; has received speaker fees from Actelion Pharmaceuticals Ltd, and Dem Pharmaceuticals; has been a clinical trial investigator for Actelion Pharmaceuticals Ltd; has received congress sponsorship from Actelion Pharmaceuticals Ltd, Bayer, Abdi Ibrahim, and Dem Pharmaceuticals; and has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. DA has received speaker fees and congress sponsorship from Actelion Pharamceuticals Ltd. SKu has been a clinical trial investigator for Lily; has received sponsorship for educational events from Nobel; and has received congress sponsorship from Sanofi and Actelion Pharmaceuticals Ltd. AA has received consultancy fees from Edwards Life Sciences; and has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. AC has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. SMC has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. LST has received consultancy fees from and served as an advisory board member for Actelion Pharmaceuticals Ltd, Amgen, Sanofi, Pfizer, Novonordisk, and MSD; has received speaker fees from Actelion Pharmaceuticals

Ltd, Amgen, Sanofi, MSD, Recordati, Kowa, Abbott, Novartis, and Mylan; has been a clinical trial investigator for Amgen, Pfizer, and Bayer; has served as a steering committee member for Amgen, and Pfizer; has received congress sponsorship from Servier, Amgen, Sanofi, and Sanovel; and has served as a steering committee member for THALES study for Actelion Pharmaceuticals Ltd. SKe is an employee of Actelion Pharmaceuticals Ltd.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by Actelion Pharmaceuticals Ltd. The steering committee was responsible for the design, concept, data management, and authorship of the study on behalf of THALES Investigators. All investigators were informed periodically about the progress of the enrollment and study results. Investigators were paid 120 TL per patient. The authors acknowledge editorial support provided by Richard McDonald and Helen Marshall of Watermeadow Medical, an Ashfield company, funded by Actelion Pharmaceuticals Ltd. It includes fees for CRO services, medical writing assistance, and editorial support.

Ethical approval

The protocol was approved by the Local Ethics Committee of Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital (Approval no: 17, Approval date: 7 November 2008) and central ethics committee of the Turkish Ministry of Health. Parental consent was obtained for patients aged <18 years.

Contributorship

MSK, CK, DA, SKu, AA, AC, SMC, and LST contributed to the concept of the study. MSK, CK, DA, SKu, AA, AC, SMC, LST, and SKe contributed to the design of the study. MSK, CK, DA, SKu, LST, and SKe contributed organizing and supervising the course of the article and took the responsibility. MSK, CK, DA, SKu, LST, and SKe took responsibility of data collection and processing of the data (experiments, patient follow-up, data management, and reporting). MSK, CK, DA, SKu, LST, and SKe took responsibility of analysis and interpretation of the data. MSK, CK, DA, SKu, and SKe took the responsibility of literature review. MSK, CK, and SKe took responsibility in the construction of the whole or body of the manuscript. MSK, CK, DA, SKu, AA, AC, SMC, LST, and SKe contributed to reviewing the article before submission not only for spelling and grammar but also for its intellectual content. All authors approved the version of the manuscript to be published.

Data availability statement

The data sharing policy of the Sponsor is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

ORCID iD

Serdar M. Kücükoglu https://orcid.org/0000-0002-3145-6209

Supplemental material

Supplemental material for this article is available online.

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