ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

# Pulmonary Arterial Hypertension and Risks of Progression

**Evgeniya Malashenko***, **Roza Vakolyuk**, **Natalia Molodozhnikova**, **Iza Berechikidze**

*I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation.*

***Corresponding Author: Evgeniya Malashenko**

## Abstract

Pulmonary arterial hypertension is an increase in blood pressure above 140 and/or 90 mmHg, caused by irreversible changes in arterioles, either by an unknown reason (essential), or as a secondary condition. 691 people under the age of 7 to 14 years (343 males and 348 females) were examined. They divided into two groups: 1st-with high blood pressure; 2nd-control group with normal blood pressure. The study results show that 19.5% of the total number of patients had high blood pressure, where 46.7%-7-10 years old children and 53.3%-11-14 years old. Almost equal ratio of boys and girls was noted in both age subgroups. Thus, there were 24.4% of boys and 22.2% of girls among children with high blood pressure aged 7-10 years and 24.4% of boys 28.9% of girls aged 11-14 years. The gender differences were found in blood pressure, heart rate and pulmonary arterial hypertension, accordingly. The systolic blood pressure (SBP) and heart rate (HR) of 7–10 years girls were significantly lower than that of male peers (96.8 and 93.2%, respectively). The most of physical development indicators of males with hypertension significantly exceeded peers with normal blood pressure. The average body weight of males with PAR significantly exceeded the control groups of the corresponding age by 16 and 25.2%, respectively, in the studied age periods. The thoracic region of the younger subgroup boys with PAH was significantly greater than that of boys with normal blood pressure by 6.5%; in the middle age subgroup - by 11.3%. The hypertension in childhood and adolescence is associated with an increase in height, weight, BMI, BFM, MM, and LBM. Hypertension occurred much more often because of overweight and obesity than with normal body weight and protein-energy malnutrition.

**Keywords:** *Pulmonary arterial hypertension (PAH), Absolute muscle mass (MM), Body mass index (BMI), lean body mass (LBM), Body fat mass (BFM).*

## Introduction

Pulmonary arterial hypertension is an increase in blood pressure above 140 and/or 90 mmHg, caused by irreversible changes in arterioles, either by an unknown reason (essential), or as a secondary condition. Pulmonary arterial hypertension (PAH), being one of the most common cardiovascular diseases, is currently an important medical and social problem [1]. The term "hypertension" corresponds to the term "essential hypertension" used in other countries and can be provided along in medical documentation and literature. The pathogenesis of essential hypertension is based on a change in arterioles: muscle hypertrophy, arteriosclerosis, loss of contractile function of both the muscle and endothelial layer of the vessel membrane.

The prevalence of PAH is very high in the world AA well as in Russia. According to international publications, the total number of people suffering from hypertension was 972 million people (303 million in developed and 669 million in developing countries), or 26.6% of men and 26.1% of women, in 2000. The number of patients with PAH is projected to be 1.6 billion by 2025 [2, 3]. The prevalence of the disease among the adult population of Russia is about 40%. PAH can lead to acute and chronic complications (cerebral disorders, coronary heart pathology, heart failure, angioretinopathy, etc.), and is one of the leading risk factors for the development of atherosclerosis and coronary heart disease (CHD).Currently, there is a reasonable opinion that a significant part of the adults with hypertension (HT) is formed from children and adolescents with high blood pressure (HBP) [4]. According to mass surveys, about 2.4 to 18% of children and adolescents suffer from PAH [5]. Occasional high blood pressure, labile hypertension and "white coat hypertension" are 2 times more frequently registered than stable PAH [6].

The pathophysiology of hypertension is mainly associated with deviations from the physiological homeostasis of the mechanisms ensure adequate blood pressure. Regulation of blood pressure is one of the most complex functions of the body, which depends on the interaction of the cardiovascular, nervous, endocrine systems and kidneys [7]. Endocrine activity is possessed not only by endocrine glands, but also by almost all functionally active tissues, e.g. vascular endothelium, lungs, juxtaglomerular apparatus, hepatocytes and even adipocytes, leptin.

Increased vascular reactivity in adolescents, which is characteristic of "white coat hypertension" (WCH), can lead to initial functional disorders and be a predictor of hypertension [6, 1].Many scholars note that PAH is associated with indicators of physical development [8, 10].

Reliable correlation coefficients between systolic blood pressure (SBP) and body weight in boys and girls were registered. A statistically significant positive correlation of the SBP with the body weight was convincingly demonstrated by Kettle index and the skinfold thickness beneath the shoulder blade in schoolchildren with hypertension. The overweight was found in 13.6% of children with hypertension and there is a direct correlation between the Kettle index and mean SBP. The higher the Kettle index, the more stable the hypertension and higher the blood pressure are.

Traditionally, anthropometric indicators in physical development include height, weight, and chest circumference. However, for assessing the physical development of children with hypertension, not only the above indicators should be considered but also body composition components. The ratio of the individual components of body weight varies significantly depending on the characteristics of nutrition and physical activity. The body composition component is a good external indicator of individual metabolic processes, that helps to evaluate various aspects of the body functioning. The goal of the research: to study the main indicators of physical development, the body composition component of children and adolescents with hypertension.

## Material and Methods

This study was performed at the Lipetsk State Pedagogical University, the Municipal Healthcare Institution "Central City Clinical Hospital" and secondary schools No. 45 and No. 47 in Lipetsk. 691 people under the age of 7 to 14 years (343 males and 348 females) were examined. They divided into two groups: $1^{st}$-with high blood pressure (HBP); $2^{nd}$-control group with normal blood pressure (NBP). The group with high blood pressure in the amount of 135 people was divided into two subgroups: the younger (7-10 years) and the middle (11-14 years).

The control group consisted of 556 people and was also divided into two age subgroups: the younger (7-10 years old) and the middle (11-14 years old). Every patient had the blood pressure and the heart rate (HR) examined. Blood pressure was measured by N. S. Korotkova method: after 5 minutes of rest, three times within 10 minutes. The minimum value obtained was taken into account.

The blood pressure was considered to be high when the SBP and/or diastolic blood pressure (DBP) was equal to or greater than the $95^{th}$ percentile for the gender, height, and age. Physical development indicators were: height (cm), weight (kg), chest circumference (CC) (cm), body mass index (BMI) (kg / $m^2$). The following were used as indicators of body composition: body fat mass (BFM) (kg), absolute muscle mass (MM) (kg), lean body mass (LBM) (kg), percentage of BFM (%), percentage of MM (%), percent LBM (%).

During the somatometric measurements, every patient had the height, weight, skinfold thickness as well as circumference of the chest, shoulder, forearm, thigh, lower leg, waist, and thighs examined. The body height, weight, and skinfold thickness were determined on the MDK-03 TP-2 "Healthy Child" medical diagnostic complex developed by Tulinovskiy Instrument-Making Plant "TVES" as part of supporting the "Healthy Child" subprogram of the federal target program "Children of Russia". Thoracic region, shoulders, forearms, hips, lower legs, circumference of waist and thighs were measured with an accuracy of 0.5 cm; as well as Waist-To-Hip-Ratio. BMI was calculated using the standard formula. The research results were processed by generally accepted mathematical and statistical methods using software systems for working with Microsoft Excel databases. The arithmetic mean (X) and the standard error of the arithmetic mean (Sx) were calculated. Student's t-test criterion was calculated for the statistically significant differences in terms of arithmetic mean values and standard error.

The relationship between the variables was detected using correlation analysis.

## Results

The study results show that 19.5% of the total number of patients had high blood pressure, where 46.7%-7-10 years old children and 53.3%-11-14 years old. Almost equal ratio of boys and girls was noted in both age subgroups (Table 1).

**Table 1: The distribution of the examined children by age subgroups and gender**

| Age, years | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | Control group | | Group of people with HBP | | Control group | | Group of people with HBP | |
| | abs. | % | abs. | % | abs. | % | abs. | % |
| 7-10 | 146 | 81.6 | 33 | 18.4 | 151 | 83.4 | 30 | 16.5 |
| 11-14 | 131 | 80.0 | 33 | 20.0 | 128 | 76.7 | 39 | 23.4 |

Thus, there were 24.4% of boys and 22.2% of girls among children with high blood pressure aged 7-10 years and 24.4% of boys 28.9% of girls aged 11-14 years

The gender differences were found in blood pressure, heart rate and pulmonary arterial hypertension (Table 2).

**Table 2: Gender characteristics of BP, HR and PAH**

| Indicator | Age, years | Gender | |
|---|---|---|---|
| | | male | female |
| SBP | 7–10 | 124.8±0.85 | 120.8±1.31* |
| | 11–14 | 128.3±1.02 | 126.0±1.34 |
| DBP | 7–10 | 79.9±1.43 | 81.8±0.98 |
| | 11–14 | 82.8±1.46 | 85.6±1.38 |
| HR | 7–10 | 93.7±2.37 | 87.3±1.66* |
| | 11–14 | 84.6±1.20 | 84.1±0.81 |

Note. Hereinafter, the differences are significant at * - p <0.05; ** - p <0.01; *** - p <0.001. The systolic blood pressure (SBP) and heart rate (HR) of 7–10 years girls were significantly lower than that of male peers (96.8 and 93.2%, respectively)

The most of physical development indicators of males with hypertension significantly exceeded peers with normal blood pressure. The average body weight of males with PAR significantly exceeded the control groups of the corresponding age by 16 and 25.2%, respectively, in the studied age periods. The thoracic region of the younger subgroup boys with PAH was significantly greater than that of boys with normal blood pressure by 6.5%; in the middle age subgroup - by 11.3%. Boys with HBP also had significant increase in BMI compared to peers with NBP: among boys aged 7-10 years-by 14.9%; among 11-14-year - by 15.5%.

Moreover, a significant increase in body height among males with PAH was found only in the middle age subgroup by 3.2% in comparison to control group. Body fat redistribution was determined by Waist-To-Hip-Ratio in the younger age group. Among boys with PAH, the most significant was an increase in BFM: by 48.7% - at 7-10 years and by 40.9% - at 11-14 years, in comparison to control group, respectively. Moreover, the total body fat percentage was significantly increased only among boys of the younger age group by 6.4% to the control group. The increase in MM was less noticeable among boys with HBP.

A significant increase was found in both age subgroups by 22.2 and 29.8% in comparison to control group, respectively. Meanwhile, an increase of percentage of muscle mass in the body was reliably registered only in boys with hypertension aged 11-14 years by 2.4%. The average LBM was also significantly higher in males of the middle age subgroup by 18.4%. However, the percentage of LBM in the body among boys with HBP was less than that in boys with NBP.

Moreover, only in the younger age subgroup, this decrease was significant compared with boys without hypertension by 6.4%, which, apparently, is explained by a greater degree of increase in the total body fat percentage.

The indicators of physical development and body composition of females with hypertension proved that they significantly exceeded peers with NBP in: height (by 4.8% - 7-10 years and by 2.7% -11-14 years), body weight (by 23.1% - 7–10 years and by 26.6% - 11-14 years), CC (by 6.5% - 7-10 years and by 9.2% - 11-14 years); BMI (by 12.7%-7-10 years and by 20.3% - 11–14 years). The total body fat percentage of girls with HBP is significantly higher compered to control group: by 42.7 and 4.8% - 7-10 years; by 43.6 and 4% - 11-14 years, respectively.

Significant differences in MM were registered. Thus, among females with hypertension of both age subgroups, the average MM was significantly higher than that of girls with NBP of the same age by 12 and 24.1%, respectively. The total percentage of muscle mass in the body of girls with HBP was less than that of the control group. However, such a decrease was significant only in the younger age subgroup by 3.5%. A significant increase in LBM was observed in study group: by 15.1% - 7-10 years and 19% for 11-14 years compere to control group, respectively.

But the percentage of LBM was significantly lower than in the control (in the younger age subgroup-by 4.8%; in the middle age subgroup-by 4%, compare to the control). Therefore, the total mass of fat and muscles increases most significantly for both genders with HBP, while the increase in bone mass according to the height and the percentage of LBM is less significant.

The gender differences data based on the physical development indicators and body composition of people with PAH shows that 7-10 years old girls' height was statistically significantly greater than boys of the same age by 4.2%. The Waist-To-Hip-Ratio for girls of both age groups is significantly lower than for male peers with HBP by 5.7 and 6%, respectively. This indicates on the predominant distribution of fat in the anterior part of the abdominal wall in boys.

The average percentage of MM in total body among females of the younger age subgroup was significantly less than among males by 6.9%. There were no significant gender differences as for the remaining studied indicators of physical development and body composition. 153 out179 boys of 7-10 years old (85.5%) had body weight corresponding to the age norm. 4 boys (2.2%) were diagnosed with protein-energy malnutrition according to BMI reduce; 19 (10.6%) were overweighed; 3 (1.7%) had obesity. 33 boys had PAH and its frequency was 18.4%.

Meanwhile, the hypertension frequency was 10.6% for boys with normal weight. 15 boys (9.8%) had stage 1 hypertension and 1 boy (0.7%) had stage 2 hypertension. 1 out of 4 boys (25%) were diagnosed with PAH in case protein-energy malnutrition. Hypertension was registered in 14 of 19 (73.7%) boys with overweight while with obesity in 2 out of 3 (67%).

Therefore, overweight due to adipopexis is essential for the occurrence of hypertension among 7-10 years old boys. 136 (82.9%) out of 164 adolescent boys (11-14 years) had a normal body weight; 4 (2.4%) had protein-energy malnutrition; 17 (10.4%) were overweighed; 7 (4.3%) had obesity. 33 patients (20.1%) had an increased blood pressure. Hypertension was in 17 people with normal body weight and its frequency was 12.5%. Therefore, 15 (11%) had stage 1 hypertension and 2 (1.5%) - stage 2 hypertension. There was no hypertension case with protein-energy malnutrition.

Hypertension was found in 10 of 17 examined patients (58.8%) with overweight, where 9 (52.9%) had stage 1 hypertension and 1 (5.9%) stage 2. Therefore, overweight is essential for the occurrence of hypertension among 11-14years old boys. The percentage of BFM exceeded 30% in both age groups with hypertension. PAH was diagnosed in 73.7% and 58.8% with overweight, while 67% and 83.3 % with obesity for 7–10 years and 11–14 years, respectively.

Whereas the frequency of hypertension was 10.5% and 12.5% with normal body weight, respectively. There were noted rare cases of hypertension in case of protein-energy malnutrition. 7-10 years old males with PAH were noted with a significantly positive correlation of SBP with physical development indicators and body components for: height, weight, BMI, CC and BFM.

Females with PAH were noted with a significantly negative correlation of SBP with the percentage of MM for: height, weight, CC, BMI, MM, LBM. Adolescent boys had a significantly positive correlation of SBP with height, MM, LBM and significantly negative to Waist-To-Hip-Ratio. Girls at this age were noted with a significantly positive correlation with height, weight, MM and LBM. Males with PAH were noted with a significantly positive correlation with most of the studied parameters at the age of 7-10 years.

Whereas, girls of the same age with PAH had such only to Waist-To-Hip-Ratio. Indicators of physical development and body composition did not correlate with DBP for adolescences; Girls with hypertension had a significantly positive correlation of heart rate with the percentage of MM, in childhood. Meanwhile, there was no significantly positive correlation of heart rate with the percentage of MM among adolescent boys. Moreover, adolescent boys with hypertension had a significantly negative correlation of heart rate with height, weight, CC, and LBM. Probably, an age-related increase in the percentage of MM is one of the factors in developing hypertension in adolescents.

Meanwhile, blood pressure and heart rate varied with age. Thus, SBP increased by 2.8% (in the control by 8.7%), DBP - by 3.6% (in the control by 14%). This reflects the tendency of changes in the processes of blood circulation regulation with both NBP and HBP and altered body composition component. Among 137 out of 181 examined girls (83.4%) aged 7-10 years, body weight corresponded to the age norm. 12 (6.6%) girls had had protein-energy malnutrition; 25 (13.8%) were overweighed; 7 (3.9%) had obesity in and 6 (3.3%)-class I obesity.

Among girls with body weight corresponding to the age norm: 123 (89.9%)had normal blood pressure; 13 (9.5%) had stage 1 hypertension; 1 (0.7%) -stage 2 hypertension. There was no hypertension case with protein-energy malnutrition. 14 girls (56%) were diagnosed with hypertension in case of overweight. 1 out of 6 girls (16.7%) had PAH in case of class I obesity while with class II obesity BP was normal. 125 (74.9%) out 167 girls aged 11-14 had the body weight corresponding to the age norm. There were 14 girls with protein-energy malnutrition (8.4%), 21 were overweighed (12.6%), 6 had obesity (3.6%), and 4 had class I obesity (2.4%), and 2-class II (1.2%). 19.2% (24 girls) with normal body weight had hypertension.

There was no hypertension case with protein-energy malnutrition. 9 girls (42.9%) had stage 1 hypertension in case of overweight. The 100% hypertension was detected in case of class I obesity moreover, stage 1 and 2 hypertensions was amounted to 50%. Therefore, overweight is less essential for the occurrence of hypertension among adolescence girls unlike boys.

Thus, 48.2% of boys aged 11-14 with HBP had overweight and obesity while for girls of this age group it was 35.1%. Meanwhile, the percentage of BFM increased by 70.8% for boys, and by 50.4% for girls; percentage of MM by 35.7 and 47.1% and percentage of LBM by 58.1 and 48.8%, respectively. The percentage of BFM of girls with HBP also exceeded 30%. PAH was diagnosed only in 56% of girls aged 7-10 and 42.9% aged 11–14 in case of overweight; in case of obesity they were 16.7 and 100%, respectively. A significantly correlation of BP with physical development indicators and body components was found for SBP mainly in childhood (Table 6). It was preserved for height, weight, CC, MM and LBM among adolescence. Heart rate was significantly positively correlated with the percentage of MM at the age of 7-10 years and with BMI at 11-14 years. Consequently, overweight is less essential for the occurrence of hypertension among girls unlike boys even having a higher percentage of BFM.

The age-related changes in the influence of the sympathoadrenal system were less noticeable in adolescent girls than in boys. SBP increased by 4.3% (in control by 3.9%), DBP - by 4.7% (in control by 4.7%), then heart rate decreased by 3.7% (in control by 5.3%) compering to a younger age subgroup.

The tendency toward a decrease in heart rate for adolescent girls with HBP may be determined by decrease in the influence of the sympathoadrenal system. Meanwhile, an increased blood pressure was supported by other mechanisms, including those associated with the body composition component modification. Thus, boys with hypertension had BFM increased by 1.7 times, MM-by 1.36 times, BLM - by 1.58 times, while girls had them by 1.49, 1.32 and 1.44 times, accordingly. The predominant accelerated increase in BFM, apparently, contributed to an increase in peripheral vascular resistance, that is one of the factors for increasing blood pressure.

## Discussion

The local cause of atherosclerosis is obviously lipid deposition under the arterial wall. A stable (at known time intervals) increase in blood pressure (BP) with excess physiological standards (at rest and under stress) and associated with it changes in the vascular wall are naturally considered to be the local causes of PAH [11].

The reason for the increase in systolic blood pressure (SBP) is the increase of blowout pressure, which is based on faster and stronger cardiac output. That is possible with chronic activation (chronic distress) of systemic and local adrenergic (sympathetic part of the autonomic nervous system, adrenal medulla, myocardial cells, baroreceptors, etc.) and related structures (renin-angiotensin-aldosterone system, vasoactive peptides) [8, 9, 12].

The increase in diastolic blood pressure (DBP) at the very beginning of the hypertension developing and the smooth muscle hypertrophy of muscle and elastic arteries are both associated with chronic increased vascular tone. A significant influence on vascular tone has an endothelial cell that is a key regulator of vascular functions. Among many other functions (multilateral humoral regulation: tissue angiotensin converting enzyme, endothelium-derived relaxing factors, etc.), endotheliocytes can locally realize neurohumoral mechanisms in providing blood to tissue, as mechanosensors (reaction to shear stress, as a function of volumetric blood flow, blood viscosity, inner diameter of the vessel, etc.) [13].

Frequent long-term increase in vascular tone is a necessary and sufficient condition for the thickening of their walls and forming of structural mechanisms for a persistent increase in peripheral vascular resistance that is associated with high DBP. Dystrophic changes in blood vessels are inseparable from these processes - the very first signs of damages are called inflammation and are inevitably followed by typical protective and adaptive reactions [14, 15].Modern view on pulmonary arterial hypertension is based on epidemiological studies, include concepts such as “target blood pressure”, which is the same for patients of all ages - less than 140 and 90 mmHg; while for patients with diabetes, the target blood pressure should be less than 130 and 80 mmHg; “risk reduce” and “CVD risk assessment and their complications”. The prevalence of hypertension is high in Russia, which is partially due to the lack of public awareness of the principles of a healthy lifestyle and poor compliance.

The asymptomatic course of hypertension, its high prevalence and the rapid development of complications require the systematic implementation of measurements of secondary (early detection) and tertiary prevention at the stage of primary medical care. A set of measurements for the treatment and supervision of a patient with hypertension by a general practitioner includes 1) an assessment of the risk of developing complications of cardiovascular diseases; 2) treatment to reduce blood pressure less than 140/90 mmHg or less than 130/80 mmHg; 3) lifestyle changes; 4) drug therapy; 5) ensuring the implementation of doctor's recommendations through instructing patients. The reasons for the unsatisfactory implementation of medical recommendations must be clarified, and methods of non-directive counseling, individual and group patient education should be used to eliminate them [16, 17].

## Conclusion

Thus, the hypertension developing during childhood and adolescence periods is associated with an increase in body height, weight, BMI, BFM, MM, LBM. The hypertension occurred much more often in case of overweight and obesity than with normal body weight and protein-energy malnutrition.

### Practical Recommendations

- All children with stable and unstable PAH should be monitored daily. According to 24-hour blood pressure monitoring results, adolescents with normal mean SBP and DBP, normal pressure-time index, but with increased variability of BP, with impaired and inconsistent circadian rhythm should be included in the high-risk group with the PAH developing and early cardiovascular complications developing.
- All adolescents with PAH are recommended to have the left ventricular mass index to be evaluate based on echo cardiogram

 

results using percentiles for body mass index by S.R. Daniels, (1999). Patients with an index of the left ventricular mass index ranged 95-99 percentile should be included in the high-risk group with the development of myocardial hypertrophy, followed by dynamic monitoring and the appointment of individual pathogenetic treatment.

- Children with an episodic increase of BP alone with aggravated heredity of hypertension and its associated diseases (pruinose, type 2 diabetes, metabolic syndrome, obesity, etc.), overweight, hyperuricemia, hypertensive retinal angiopathy should be included to the high-risk group of the development of hypertension.
- All children with AH syndrome should be determined by psycho-characterological accentuations using a Personality Pathology-Basic Questionnaire. Children with the dominance of sensitive character, a high level of neuroticism, a high level of personal and reactive anxiety should be included in the high-risk group of the development of hypertension and have rehabilitation together with a psychologist.

## References


1. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, Chaouat A (2017) Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. European Respiratory Journal, 50(2): 1700889.
2. Dafni U (2011) Landmark analysis at the 25-year landmark point. Circulation: Cardiovascular Quality and Outcomes, 4(3): 363-371.
3. Raina A, Humbert M (2016) Risk assessment in pulmonary arterial hypertension. European Respiratory Review, 25(142): 390-398
4. Frost AE, Badesch DB, Miller DP, Benza RL, Meltzer LA, McGoon MD (2013) Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL Registry analysis. Chest, 144(5): 1521-1529.
5. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Oudiz RJ (2015a) Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. New England Journal of Medicine, 373(9): 834-844.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Ghofrani A (2015b) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European heart journal, 37(1): 67-119.
7. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Ghofrani A (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur. Heart J., 37: 67-119.
8. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, Frost AE, Torbicki A (2004) End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. Journal of the American College of Cardiology, 43(12): S48-S55.
9. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, Distler O (2017) Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. European Respiratory Journal, 50(2): 1700740.
10. Gomberg-Maitland M, Bull TM, Saggar R, Barst RJ, Elgazayerly A, Fleming TR, Ventura C (2013) New trial designs and potential therapies for pulmonary artery hypertension. Journal of the American College of Cardiology, 62(25): D82-D91.
11. Anderson JR, Cain KC, Gelber RD (1983) Analysis of survival by tumor response. J. Clin Oncol., 1(11): 710-719.
12. Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, Rådegran G (2017) A comprehensive risk


 

stratification at early follow-up determines prognosis in pulmonary arterial hypertension. European heart journal, 39(47): 4175-4181.

13. McLaughlin VV, Badesch DB, Delcroix M, Fleming TR, Gaine, SP, Galiè N, Provencher S (2009) End points and clinical trial design in pulmonary arterial hypertension. Journal of the American College of Cardiology, 54(1 Supplement), S97-S107.
14. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Rubin LJ (2015) Selexipag for the treatment of pulmonary arterial hypertension. New England Journal of Medicine, 373(26): 2522-2533.
15. Sitbon O, Sattler C, Bertoletti L, Savale L, Cottin V, Jaïs X, Bouvaist H (2016) Initial dual oral combination therapy in pulmonary arterial hypertension. European Respiratory Journal, 47(6): 1727-1736.
16. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Hoeper MM (2012) The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. European Respiratory Journal, 39(3): 589-596.
17. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Mittelholzer CM (2013) Macitentan and morbidity and mortality in pulmonary arterial hypertension. New England Journal of Medicine, 369(9): 809-818.