Six-minute walk test in pulmonary arterial hypertension

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ABSTRACT

Exercise intolerance is the main characteristic of pulmonary arterial hypertension (PAH). The six-minute walk test (6MWT) and cardiopulmonary exercise test are widely used in assessing exercise capacity of PAH patients. Six-minute walk distance (6MWD) has been specified as the main clinical outcome in PAH and has been used as the primary end-point in many studies conducted for new PAH treatments. Using 6MWD as the end-point in clinical studies has many advantages. 6MWT is an inexpensive, easily applicable, and repeatable standardized test that is well-tolerated by PAH patients. Moreover, it is a valid measure of symptomatic improvement. It is correlated with variables of maximal cardiopulmonary exercise test as a measure of submaximal exercise capacity and disease severity markers such as functional class and pulmonary hemodynamics. It is widely used in clinical practice together with other invasive and non-invasive disease markers in assessing disease progression and response to treatment. In addition, it has prognostic importance and is a good prognostic marker. On the other hand, there are limitations to the use of 6MWD as the primary end-point in PAH treatment. It has decreased sensitivity in individuals with less severe disease and high 6MWD at baseline and decreased adequacy in assessing the effects of treatment in patients who are still under PAH treatment. Despite the limitations, 6MWD plays a key role in the evaluation and management of PAH patients. *(Anatol J Cardiol 2015; 15: 249-54)*
Keywords: pulmonary arterial hypertension, six-minute walk test, six-minute walk distance, exercise test

Introduction

Pulmonary arterial hypertension (PAH) is a rarely encountered disease that is characterized by a progressive increase in pulmonary vascular resistance and arterial pressure, leading to right heart failure and premature death (1-3). Exercise intolerance is the main characteristic of pulmonary hypertension. Determination of exercise capacity has an important role in the evaluation of patients. Exercise capacity measured by six-minute walk distance (6MWD) and hemodynamic parameters such as right atrium pressure gender, and cardiac output were observed to be the significant markers of survival in the French Registry (4). Exercise tests commonly used for evaluation include the six-minute walk test (6MWT), standard treadmill exercise test performed using low-intensity exercise protocol, cardiopulmonary exercise test (CPET) performed by gas-exchange measurement, exercise test performed simultaneously with Doppler echocardiography, and exercise test performed simultaneously with right heart catheterization. These tests assess different physiological parameters. 6MWT and CPET are the most frequently used tests in clinical practice (3, 5, 6).

6MWT is an inexpensive and simple test, technically easy to apply, repeatable, convenient to use in large patient groups, reflects daily living activities better than laboratory tests, and is well-tolerated by patients (7, 8). However, it has disadvantages such as its dependency on patient effort and unavailability to measure gas exchange and ventilation efficacy (8). 6MWT is influenced by many factors including age, height, weight, gender, ethnicity, comorbid conditions, supplemental O_2 use, encouragement level, corridor length used for testing, learning effect, and mood (9, 10). In 2002, the American Thoracic Society published a guideline on the standardization of 6MWT. According to this guideline, the patient rests for at least 10 min prior to 6MWT, and the dose and timing of medications that the patient has been receiving are recorded. Heart rate, blood pressure, and oxygen saturation (SO_2) are measured, and level of tiredness and dyspnea are determined according to the Borg scale both before and after the test. Resting period, if any, and the reason and other symptoms are recorded at the end of the test. 6MWD

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is determined, and the percent of predicted value is calculated (10). According to the guidelines of the European Society of Cardiology and European Respiratory Society (ESC/ERS) published in 2009, 6MWT should be performed at baseline and repeated 3-4 months after the beginning or modification of treatment and when the clinical condition worsens; in addition, regular monitoring should be performed every 3-6 months in stable patients (11).

6MWT is used to determine functional exercise capacity, assess treatment efficacy, predict prognosis, and establish rehabilitation programs in PAH patients.

In this review, we will be dealing with the role of 6MWD in the determination of functional exercise capacity, treatment assessment, and prognostic evaluation.

Functional capacity, disease severity, and six-minute walk test

Functional capacity is substantially restricted in PAH patients. Distance covered in 6MWT significantly decreased in proportion to the severity of New York Heart Association functional class (FC). Data obtained from registry studies performed in France, United States, China, and Spain demonstrated that the mean 6MWD of PAH patients is between 329 and 378 m, with higher values in patients with FC I-II (12). Besides, the French registry reported that 6MWD varied between 36% and 68% of the predicted distance in PAH patients and showed that patients with FC III and IV had significantly lower 6MWD compared with patients in FC I-II. (13). Similar results were reported in different studies (14, 15). In a study from Turkey, the mean 6MWD was found to be 184 m with the highest values (201 m) observed in the patient group with PAH associated with congenital heart disease and the lowest value (159 m) observed in the patient group in PAH associated with connective tissue diseases (16). In another study, Güngör et al. (17) reported that mean 6MWD was 347 m in patients with Eisenmenger syndrome.

Response to treatment and six-minute walk test

Treatment options for PAH patients have significantly improved in the last 20 years in line with the approval of effective PAH-specific drugs (7, 18). All currently available oral therapies for the treatment of PAH have been approved based on 6MWD changes in a 12–16-week study period. At the end of approximately 12-week treatment period, significant improvement was reported in 6MWD, changing between 10 and 84 m (3%-21%) with three groups of drugs-prostacyclins, endothelin receptor antagonists, and phosphodiesterase inhibitors-used in the treatment of PAH (19).

6MWT has been used as the primary end-point in all placebo-controlled studies on PAH since the earliest intravenous epoprostenol study conducted 20 years ago and that had been the basis for the approval of currently available medical therapies. In the majority of those studies, secondary measurements such as pulmonary hemodynamic parameters, cardiac markers, quality of life parameters, and clinical worsening were evaluated, and the relation between exercise capacity improvement and other clinically relevant parameters was found to be variable (7, 15, 20-31). Whereas some studies found that the increase in 6MWD is in line with the improvement in hemodynamic parameters (20, 23, 25-28, 30, 31), others failed to demonstrate such a relation (21, 29). On the other hand, Savarese et al. (32) in their meta-analysis comprising 12 studies, reported a significant inverse correlation between the changes in 6MWD and pulmonary vascular resistance (r=-0.63, p=0.009).

Degano et al. (14), with treatment, reported a significant improvement in the WHO functional class and hemodynamic parameters in PAH patients with 6MWD over 450 m without a significant change in 6MWD. Researchers concluded that hemodynamic parameters and functional class are more sensitive than 6MWD in determining the changes secondary to PAH-specific treatment in patients with a 6MWD over 450 m (14).

Recent phase III studies performed in the last 5 years for PAH-specific new drugs such as macitentan, selexipag, riociguat, and imatinib showed similar improvements in 6MWD (33). An average 24.7 m increase from baseline in 6MWD in patients receiving selexipag was insignificant when compared with placebo (34). It was observed that 12-week riociguat therapy (PATENT-1 study) was well-tolerated and provided a significant increase by 36 m in 6MWD (35). In the Phase III IMPRES study, imatinib, which was used as an additional therapy, provided a significant increase (32 m) in exercise capacity in PAH patients but had no benefit in terms of functional class, time to clinical worsening, and mortality (36).

Because disease progression may change among patients, target values and treatment goals must be tailored (37). The new therapeutic goal for 6MWD in PAH patients has been accepted to be 380-440 m. Although a 6MWD over 400 m is an acceptable value for many PAH patients, it was reported that this may not be adequate in young patients (7). Younger patients may mostly walk a distance over 500 m despite severe PAH (37). It has been suggested that the predicted percent may better reflect the appropriate treatment goal for some patients. Treatment goals for scleroderma patients, which is one of the subgroups of PAH, have not been defined clearly. Functional targets such as 6MWD may not be reliable for such patients because of the systemic nature of scleroderma. It was reported that results are better for PAH patients with systemic lupus erythematous in comparison to PAH patients with scleroderma (7).

Prognosis and six-minute walk test

Studies have revealed that 6MWD is also an independent determinant of survival (37); it was concluded that a low 6MWD is associated with an increased risk for survival and that a high 6MWD is associated with a low risk for survival (4, 12, 38). According to the latest ESC/ERS guidelines, a 6 MWD over 500 m indicates good prognosis, whereas a 6MWD less than 300 m indicates poor prognosis (11).

There are three 6MWD parameters, of which the relation with post-treatment outcomes has been evaluated in PAH

patients: 1- Baseline 6MWD, 2- 6MWD assessed at a predefined time after the onset of treatment, and 3- Change in 6MWD observed after treatment. These parameters have different validities as a prognostic indicator (39).

Baseline six-minute walk distance (before treatment)

Among patients treated with epoprostenol for 12 weeks, significantly lower baseline 6MWD was reported in 8 patients who died at the end of the study compared with 73 patients who were still alive (195 m vs. 305 m; p<0.003) (23). Strikingly, similar results were found after years in the epoprostenol and sildenafil combination study. While the mean 6MWD of 7 patients who died over the course of a 16-week study was 182 m, it was reported to be 354 m for the overall study population (20). Analysis of data on survival derived from patient cohorts in Japan and France revealed strong supporting data on the relation between prognosis and baseline 6MWD (15, 24, 40). A single-center study from Japan reported significantly better survival rates for patients with 6MWD 332 m or more among those under prostacyclin therapy (15). Likewise, in a single-center study in France on patients treated with bosentan, there was a significant difference between the survival rates of patients with 6MWD less than and more than 330 m (24). Paciocco et al. (41) reported that mortality risk is enhanced by 2.4-fold if the baseline walking distance is 300 m or less and that each additional 50 m walking distance decreases the risk of mortality by 18%. Furthermore, they concluded that a decrease higher than 10% in SO_2 during 6MWT indicates approximately 3-fold higher mortality. Multidimensional analysis of data obtained from 178 patients who were treated with epoprostenol between 1992 and 2001 in France demonstrated that patients with a baseline 6MWD of 250 m and less have 2.2-fold higher mortality risk compared with those who were able to walk more than 250 m (40). Moreover, single and multiple analyses of data from the national French registry study for PAH revealed a significant relation between baseline 6MWD and survival (4). In a meta-analysis comprising approximately 2000 patients and 16 randomized studies, Macchia et al. (42) reported that there was a significant relation between baseline 6MWD (less than 330 m in particular) and fatal events during follow-up and that prognosis worsens progressively. In the majority of analyses, the "cut-off" value for baseline 6MWD, which is used to determine survival, is 330 m. The "cut-off" value used in data analysis influences the outcomes. Fritz et al. (43) stated that a baseline 6MWD less than 250 m in PAH patients is associated with a mortality risk of approximately 50% within 2 years. It was observed that mortality risk is 8% in patients with a higher baseline 6MWD. On the other hand, 250 m is a very low threshold for 6MWD. When this threshold was increased, very little difference was observed between patients with a baseline 6MWD over 288 m and over 415 m in terms of mortality risk. In a recent study, Groepenhoff et al. (44) reported that baseline 6MWD is an indicator of survival in idiopathic PAH patients. In another study, it was observed that baseline 6MWD and SO_2 are markers of mortality over the course of 3.3-year follow-up period in patients with Eisenmenger syndrome. Researchers concluded that patients who were unable to achieve a 6MWD of 350 m or those having a baseline SO_2 lower than 85% had a 3-fold higher risk of mortality (45). On the other hand, in 226 consecutive patients studied by Wensel et al. (46), 6MWD was a non-significant prognostic marker; however, in this study, only 52% of the patients performed 6MWT at baseline.

Six-minute walk distance achieved after treatment

The distance achieved after treatment has been shown to be a prognostic marker in several studies (24, 40, 43). After 3-month epoprostenol therapy, better survival rates were achieved in patients with a 6MWD of 380 m and higher compared with those who could not reach this threshold (40). Likewise, Provencher et al. (24) observed better survival rates after 4 months of bosentan therapy in patients who reached a threshold higher than 378 m compared with patients who could not walk that distance. One-, two-, and three-year survival rates of patients who were able to walk more than 378 m were 100%, 100%, and 90% respectively, whereas the corresponding percentages were 85%, 79%, and 69%, respectively for patients who walked less than 378 m (p=0.005). In the ARIES study, it was reported that the risk of mortality decreased over the course of a 2-year follow-up period after 12-week ambrisentan therapy in patients with 6MWD higher than 323 m compared with patients who were unable to reach that threshold (p<0.001). When the results of this cohort were evaluated, 6MWD achieved after 12 months of treatment was not found to be a better marker than baseline 6MWD (43). On the other hand, retrospective analysis of the patients who received subcutaneous treprostinil revealed that post-treatment 6MWD was not linearly correlated with survival; however, even in this study a walking distance of 295 m or less after 12 weeks was correlated with a significant decrease in survival over the course of 3-year follow-up period (3-year survival rate was 57% in patients with a 6MWD of 295 m or less, 77% in patients with a 6MWD between 296 and 351 m, 77% in patients with 6MWD between 352 and 405 m, and 81% in patients with 6MWD higher than 405 m) (47).

Change in six-minute walk distance after treatment compared with baseline values

Studies have revealed inconsistency between the change in 6MWD and clinical outcome. Groepenhoff et al. (44) reported that change in 6MWD in IPAH patients after a 13-month treatment period is the determinant of survival. In another study, Benza et al. (47) analyzed the determinants of 3-year survival in patients treated with subcutaneous treprostinil and reported that an increase by more than 20 m in 6MWD with 12-week treprostinil therapy is associated with higher survival rates when compared with increases lower than that (80% vs 69%, p=0.039) and that each 20 m increase in 6MWD shows a positive correlation with survival.

On the other hand, it has been reported that there is no difference between individuals with and without 112 m or more

increase in 6MWD after 3-month epoprostenol therapy in terms of survival (40). A significant increase in 6MWD was not found to be associated with a significant improvement in parameters such as time to clinical worsening (25, 48). Systematic reviews and meta-analysis studies that comprise randomized studies performed with PAH-specific therapies have demonstrated that a change in 6MWD after treatment compared with baseline values does not determine survival benefit (42) or incidence of clinical events (32). In a meta-analysis including 10 randomized controlled studies and more than 2000 patients that investigated whether changes in 6MWD over the course of a 12-week treatment period were correlated with clinical events, Gabler et al. (49) found that changes in 6MWD were correlated with treatment and clinical outcome but that it explained only 22% of the treatment effect. In addition, they reported that a change by 41.8 m in 6MWD is associated with a significant decrease in the incidence of clinical events but that threshold decreases to 25.7 m when the patients who received prior treatment were excluded from the analysis. Researchers concluded that changes in 6MWD could not determine the majority of the treatment effect and may have only minimum validity as an end point for clinical events. In a new meta-analysis comprising 22 randomized controlled studies and 3112 patients, it was observed that change in 6MWD is not correlated with long-term outcomes (32).

Limitations and questions to be answered

Although 6MWD has been used as the end-point in most of the studies, there are limitations against the use of 6MWD as the primary end-point (50). The use of combined primary endpoints under the name of clinical worsening has been suggested because of the limitations of 6MWD (8). In their recent review, Gaine et al. (39) discussed the limitations of 6MWD and stated that 6MWD has decreased sensitivity in patients with milder symptoms who walked longer distance (ceiling effect) and decreased adequacy in patients who were still under PAH treatment. The ceiling effect in 6MWD may mask the efficacy in patients who have longer walking distance at baseline but significant pathology as has been shown in the bosentan study in functional class II patients (39). It is difficult to determine the changes in walking distance in patients with baseline 6MWD higher than 450 m. It was observed that 6MWD was higher than 450 m in some patients who had severe hemodynamic changes at the time of PAH diagnosis (13). Furthermore, additional treatment may not provide further gains in patients who already had improvement in their exercise capacity on a background therapy. The great majority of studies that were used for analysis consisted of treatment-naïve individuals. In treatment-naïve patients, higher improvement is likely to occur in patients receiving active treatment; contrarily, the group receiving placebo remains unchanged or even worsens. Therefore, treatment effect becomes greater compared with placebo. Different in combination studies, the magnitude of improvement may decrease because of the active drug being added to the existing treatment. The PHIRST study analysis showed the importance of this effect reporting a lower increase in 6MWD in patients who received tadalafil in addition to their existing treatment compared with patients who received tadalafil alone (51). This effect should be taken into account when new drugs are tested as additional effective treatments in patients who receive the currently available PAH drugs (22).

What the real significant difference in walking distance beyond reaching statistical significance is one of the weaknesses in assessing 6MWD. First, Gilbert et al. (52) reported that the minimal important difference in 6MWD is 41 m in patients treated with sildenafil. In another study, Mathai et al. (53) reported that the minimal important difference in 6MWD is 33 m in PAH patients. Similar but a more comprehensive analysis was done by Gabler et al. (49), and the outcomes of 10 randomized clinical studies revealed that significant threshold effect in decreasing the incidence of clinical events is 41.8 m.

Another weakness of 6MWT is the fact that it provides less information on the mechanisms of exercise restriction. CPET would give more information on the organs or systems that contribute to decreased exercise tolerance. Despite the absence of definite contraindications for 6MWT, it would be more appropriate to evaluate patients with prior unstable angina or myocardial infarct in the last month or patients who have significant exercise-associated symptoms (e.g., syncope) using CPET, which has more intensive monitoring conditions (9).

Because of reasons that are not associated with PAH, the specificity of 6MWD, as a measurement of exercise capacity, may be striking particularly in low walking distances. For example, the walking distance of a scleroderma patient may be low as a result of weakness and other comorbidities. An out of condition state, loss of muscle tone, and endurance may be seen in individuals with chronic disease and may influence the distance the individual is able to walk (39).

There are a few questions that have not been answered yet on the use of 6MWD. The questions include which distance best correlates with exercise capacity and right heart function and whether this has been measured as the absolute value of 6MWD associated with improved survival in PAH (7). Lee et al. (54), who interpreted whether the distance can be evaluated according to the percent predicted based on patient parameters (age, height, gender), reported that the percent predicted 6MWD may help clinicians with the interpretation of 6MWT but that its prognostic value is not superior to the absolute 6MWD.

Conclusion

In conclusion, 6MWT is a cheap, inexpensive, and repeatable test, which is technically easy to apply, appropriate for large patient groups, and well-tolerated by the patients. Despite various limitations, it should be kept in mind that 6MWD plays a key role in the evaluation and treatment of PAH patients together with symptom monitoring, functional class assessment, hemodynamic parameters, and biological markers. However, recently completed trials studying patients on background therapies sug-

gest that clinical worsening showing morbidity and mortality may be a more suitable and meaningful primary end-point than 6MWD.

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References

1. Guillevin L, Armstrong I, Aldrighetti R, Howard LS, Ryftenius H, Fischer A, et al. Understanding the impact of pulmonary arterial hypertension on patients' and careers' lives. Eur Respir Rev 2013; 22: 535-42. [CrossRef]
2. Küçükoğlu MS, Başkurt M. Pulmonary hypertension: diagnosis and clinical classification. Anatol J Cardiol 2010; 10(Supp 1): 2-4. [CrossRef]
3. Yurdakul S, Aytekin S. Diagnostic algorithms in pulmonary hypertension. Anatol J Cardiol 2010; 10(Supp 1): 14-26. [CrossRef]
4. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010; 122: 156-63. [CrossRef]
5. Can MM, Kaymaz C. Clinical end-points and surrogate markers of pulmonary arterial hypertension in the light of evidence-based treatment. Anatol J Cardiol 2010; 10(Supp 1): 36-42. [CrossRef]
6. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126(Suppl 1): 14-34. [CrossRef]
7. McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013; 62(Suppl 25): 73-81. [CrossRef]
8. McLaughlin VV, Badesch DB, Delcroix M, Fleming TR, Gaine SP, Galie N, et al. Endpoints and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54(Suppl 1): 97-107. [CrossRef]
9. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J 2009; 39: 495-501. [CrossRef]
10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-7. [CrossRef]
11. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34: 1219-63. [CrossRef]
12. McGoon MD, Benza RL, Escribano-Subios P, Jiang X, Miller DP, Peacock AJ, et al. Pulmonary arterial hypertension. Epidemiology and registries. J Am Coll Cardiol 2013; 62: 51-9. [CrossRef]
13. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-30. [CrossRef]
14. Degano B, Sitbon O, Savale L, Garcia G, O'Callaghan DS, Jais X, et al. Characterization of pulmonary arterial hypertension patients walking more than 450 m in 6 min at diagnosis. Chest 2010; 137: 1297-303. [CrossRef]
15. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000; 161: 487-92. [CrossRef]
16. Tokgözoğlu L, Akdoğan A, Okutucu S, Kaya EB, Aytemir K, Özkutlu H. Two years of multidisciplinary diagnostic and therapeutic experience in patients with pulmonary arterial hypertension. Turk Kardiyol Dern Ars 2009; 37: 378-93.
17. Güngör H, Ertugay S, Ayık MF, Demir E, Engin C, Yağdı T, et al. Clinical and hemodynamic features of Eisenmenger syndrome patients at the time of first admission: a tertiary referral-center experience. Anatol J Cardiol 2012; 12: 11-5.
18. Okutucu S, Tokgözoğlu L. Therapeutic algorithms in pulmonary hypertension in the light of current guidelines. Anatol J Cardiol 2010; 10(Supp 2): 19-26. [CrossRef]
19. Demir R, Küçükoğlu MS. Evaluation of exercise capacity in pulmonary arterial hypertension. Turk Kardiyol Dern Ars 2010; 38: 580-8.
20. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med 2008; 149: 521-30. [CrossRef]
21. Galie N, Humbert M, Vachiery JL, Vizza CD, Kneussl M, Manes A, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized double-blind, placebo-controlled study. J Am Coll Cardiol 2002; 39: 1496-502. [CrossRef]
22. Rubin LJ. The 6-minute walk test in pulmonary arterial hypertension: how far is enough? Am J Respir Crit Care Med 2012; 186: 396-7. [CrossRef]
23. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996; 334: 296-301. [CrossRef]
24. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006; 27: 589-95. [CrossRef]
25. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169: 441-7. [CrossRef]
26. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galie N, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol 2007; 34: 2417-22.
27. Jing ZC, Yu ZX, Shen JY, Wu BX, Xu KF, Zhu XY, et al. Vardenafil in pulmonary arterial hypertension: a randomized double-blind, placebo-controlled study. Am J Respir Crit Care Med 2011; 183: 1723-9. [CrossRef]
28. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322-9. [CrossRef]
29. Ghofrani HA, Morrell NW, Hooper MM, Olschewski H, Peacock AJ, Barst RJ, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med 2010; 182: 1171-7. [CrossRef]

30. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006; 174: 1257-63. [CrossRef]
31. Oudiz RJ, Schilz RJ, Barst RJ, Galie N, Rich S, Rubin LJ, et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest 2004; 126: 420-7. [CrossRef]
32. Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension. A meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012; 60: 1192-201. [CrossRef]
33. Galie N, Ghofrani AH. New horizons in pulmonary arterial hypertension therapies. Eur Respir Rev 2013; 22: 503-14. [CrossRef]
34. Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlocai K, Galie N, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012; 40: 874-80. [CrossRef]
35. Ghofrani HA, Galie N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369: 330-40. [CrossRef]
36. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galie N, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013; 127: 1128-38. [CrossRef]
37. Vachiery JL, Yerly P, Huez S. How to detect disease progression in pulmonary arterial hypertension. Eur Respir Rev 2012; 123: 40-7. [CrossRef]
38. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension. Insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010; 122: 164-72. [CrossRef]
39. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. Eur Respir Rew 2013; 22: 487-94. [CrossRef]
40. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40: 780-8. [CrossRef]
41. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubinfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001; 17: 647-52. [CrossRef]
42. Macchia A, Marchioli R, Marfisi R, Scarano M, Levantesi G, Tavazzi L, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007; 153: 1037-47. [CrossRef]
43. Fritz JS, Blair C, Qudiz RJ, Dufton C, Olschewski H, Despain D, et al. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. Chest 2013; 143: 315-23. [CrossRef]
44. Groepenhoff H, Vonk-Noordegraaf, van de Veerdonk MC, Boonstra A, Westerhof N, Bogaard HJ. Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. PLoS One 2013; 8: e72013. [CrossRef]
45. Kempny A, Dimopoulos K, Alanso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A, et al. Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol 2013; 168: 4784-9. [CrossRef]
46. Wensel R, Francis DP, Meyer FJ, Opitz CF, Bruch L, Halank M, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 2013; 167: 1193-8. [CrossRef]
47. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. J Heart Lung Transplant 2011; 30: 982-9. [CrossRef]
48. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353: 2148-57. [CrossRef]
49. Gabler NB, French B, Strom BL, Palevsky HI, Taichman DB, Kawut SM, et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. Circulation 2012; 126: 349-56. [CrossRef]
50. Rubin LJ, Galie N, Simonneau G, McLaughlin V. A paradigm shift in pulmonary arterial hypertension management. Eur Respir Rew 2013; 22: 423-6. [CrossRef]
51. Barst RJ, Oudiz RJ, Beardsworth A, Brundage BH, Simonneau G, Ghofrani HA, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. J Heart Lung Transplant 2011; 30: 632-43. [CrossRef]
52. Gilbert C, Brown MC, Cappelleri JC, Carlsson M, McKenna SP. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil. Chest 2009; 135: 137-42. [CrossRef]
53. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2012; 186: 428-33. [CrossRef]
54. Lee WT, Peacock AJ, Johnson MK. The role of percent predicted 6-min walk distance in pulmonary arterial hypertension. Eur Respir J 2010; 36: 1294-301. [CrossRef]