

Directing therapy in pulmonary arterial hypertension using a target 6 min walk distance

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BACKGROUND: The most effective approaches to escalating advanced therapies in pulmonary arterial hypertension (PAH) are controversial.

OBJECTIVE: To compare outcomes before and after introducing a target 6 min walk distance (6MWD) treatment strategy in PAH using registry data.

METHODS: From 2001 to 2005, WHO class II to IV patients were treated with bosentan or prostanoids. In July 2005, a target 6MWD strategy was adopted. Monotherapy continued if 6MWD remained >350 m. For patients in whom 6MWD was ≤350 m, sildenafil was added. If 6MWD remained <350 m, prostanoids were considered. Changes in 6MWD, WHO class and survival rate were compared between periods.

RESULTS: Before using the 6MWD strategy, there was a statistically significant improvement in mean WHO class at six, nine and 12 months (2.5±0.8 [P<0.015]; 2.5±0.8 [P<0.005]; and 2.5±0.9 [P<0.03], respectively) compared with baseline (2.9±0.9). There was a statistically significant increase in mean 6MWD at three, six, nine and 12 months (383±113 m [P<0.005]; 401±102 m [P<0.006]; 400±109 m [P<0.001]; and 399±110 m [P<0.004], respectively) compared with baseline (321±119 m). The survival rate was 95% at one and two years. From 2005 to 2009, there was a statistically significant improvement in mean WHO class at three, six, nine and 12 months (2.6±0.8 [P<0.05]; 2.3±0.9 [P<0.0001]; 2.3±0.9 [P<0.0001]; and 2.3±1.0 [P<0.0005], respectively) compared with baseline (2.8±0.7). There was statistically significant improvement in 6MWD at six months (381±126 m [P<0.05]), followed by a decline toward baseline (354±117 m). One- and two-year survival rates in the 6MWD target era were 95% and 80%, respectively.

CONCLUSION: Based on registry data, adoption of this strategy did not affect survival rates, nor cause a sustained improvement in 6MWD by 12 months. WHO class improved similarly in both treatment groups.

Key Words: *Pulmonary arterial hypertension; Registry; Therapy*

Pulmonary arterial hypertension (PAH) is characterized by progressive narrowing of precapillary pulmonary vessels leading to right ventricular failure. Subtypes of PAH include idiopathic and familial; PAH may also be associated with conditions such as connective tissue disease (CTD), congenital heart disease, portal hypertension, HIV infection and exposures to drugs such as anorexigens. Of the PAH subtypes, idiopathic PAH (IPAH) has been studied most extensively. Epidemiological data demonstrate that without treatment, the median duration of survival in IPAH is approximately 2.8 years from the date of diagnosis (1).

Although treatment options have greatly improved patient outcomes in PAH over the past several years, the most effective strategy for using the available treatments is not proven. Epoprostenol, introduced in 1994 for the treatment of PAH, is the only drug to demonstrate a survival benefit in a prospective, randomized, placebo-controlled study (2). However, it is a cumbersome treatment with disadvantages and potential for serious harm. The introduction of the oral endothelin receptor antagonist bosentan in 2001 dramatically changed the treatment of PAH. This medication has shown improvement in 6 min

L'orientation du traitement de l'hypertension artérielle pulmonaire d'après un résultat ciblé au test de marche de 6 minutes

HISTORIQUE : Les démarches les plus efficaces pour intensifier les thérapies avancées de l'hypertension artérielle pulmonaire (HTAP) sont controversées.

OBJECTIF : Comparer l'issue avant et après l'adoption d'une stratégie thérapeutique établissant un résultat ciblé au test de marche de 6 minutes (TM6M) en cas d'HTAP, au moyen des données d'un registre.

MÉTHODOLOGIE : De 2001 à 2005, des patients des classes II à IV de l'OMS ont reçu un traitement au bosentan ou aux prostanoides. En juillet 2005, on a adopté une stratégie de résultat ciblé au TM6M. La monothérapie était maintenue si le TM6M demeurait supérieur à 350 m. Chez les patients dont le TM6M était égal ou inférieur à 350 m, on ajoutait du sildénafil. Si leur TM6M demeurait inférieur à 350 m, on envisageait d'amorcer les prostanoides. On comparait les modifications au TM6M, à la classe de l'OMS et au taux de survie entre les périodes.

RÉSULTATS : Avant d'utiliser la stratégie du TM6M, on constatait une amélioration statistiquement significative de la classe moyenne de l'OMS à six, neuf et 12 mois (2,5±0,8 [P<0,015], 2,5±0,8 [P<0,005] et 2,5±0,9 [P<0,03], respectivement) par rapport aux données de départ (2,9±0,9). On constatait une amélioration statistiquement significative du TM6M moyen à trois, six, neuf et 12 mois (383±113 m [P<0,005], 401±102 m [P<0,006], 400±109 m [P<0,001] et 399±110 m [P<0,004], respectivement) par rapport aux données de départ (321±119 m). Le taux de survie était de 95 % au bout de un et deux ans. De 2005 à 2009, on constatait une amélioration statistiquement significative de la classe moyenne de l'OMS à trois, six, neuf et 12 mois (2,6±0,8 [P<0,05], 2,3±0,9 [P<0,0001], 2,3±0,9 [P<0,0001] et 2,3±1,0 [P<0,0005], respectivement) par rapport aux données de départ (2,8±0,7). On constatait une amélioration statistiquement significative du TM6M à six mois (381±126 m [P<0,05]), suivie d'une diminution vers les données de départ (354±117 m). Les taux de survie au bout de un et deux ans pendant la période de résultat ciblé du TM6M s'élevaient à 95 % et 80 %, respectivement.

CONCLUSION : D'après les données d'un registre, l'adoption de cette stratégie n'avait pas d'influence sur le taux de survie et ne suscitait pas une amélioration soutenue du TM6M au bout de 12 mois. La classe de l'OMS s'améliorait de manière similaire dans les deux groupes de traitement.

walk distance (6MWD), WHO functional class and time to clinical worsening (3-5). A second class of oral therapy, the phosphodiesterase inhibitors – sildenafil and tadalafil – became available to some centres for treatment of PAH as early as 2005. They have since been approved for treatment of patients with PAH in WHO functional class II or III (6,7).

As increasing options for treatment became available, the correct use and application of these treatments has been investigated. Before 2006, many centres used monotherapy with endothelin antagonists, phosphodiesterase inhibitors or prostanoids. As of January 2006, the treatment approach shifted to include combination therapy (8). Many centres also began using goal-based treatment approaches including quality of life, WHO functional class, 6MWD, cardiopulmonary exercise test parameters, hemodynamic measurements and survival. For example, Hooper et al (9) studied a goal-oriented treatment strategy using combinations of bosentan, sildenafil and inhaled iloprost in patients with severe PAH. Treatment goals were defined as a 6MWD distance >380 m, a peak oxygen uptake >10.4 mL/min/kg during cardiopulmonary exercise testing and peak systolic blood pressure

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>120 mmHg during exercise. Patients were initiated on bosentan monotherapy. If all three goals were not met on two consecutive follow-up visits, sildenafil was added, followed by inhaled iloprost if needed. Treatment according to this protocol resulted in survival rates at one, two and three years of 93%, 83.1% and 79.9%, respectively, which was significantly better than survival rates in a historical control group.

The present study examined the outcomes of patients followed in a PAH clinic before and after the introduction of a simple treatment strategy based on a target 6MWD using registry data collected in a single tertiary care pulmonary hypertension clinic. Specifically, change in 6MWD, change in WHO functional class and survival were compared between the two time periods.

METHODS

The Pulmonary Hypertension Clinic at the Health Sciences Centre in Winnipeg, Manitoba, serves as a tertiary care referral centre for patients with pulmonary hypertension from a geographical catchment area including Manitoba, Nunavut, northwestern Ontario and parts of Saskatchewan. Starting in 2000, pulmonary hypertension patients receiving care in the Winnipeg clinic were enrolled in a local pulmonary hypertension registry approved by the University of Manitoba Research Ethics Board. Patient information was recorded at initial presentation and prospectively updated at each follow-up assessment, including diagnostics, demographics, 6MWD, medications, WHO functional class, complications, lung transplantation and death. All patients underwent right heart catheterization following their initial assessment, provided it was not performed before referral. Diagnostic criteria for PAH were consistent with the National Institutes of Health definition: mean pulmonary artery pressure >25 mmHg at rest with a normal pulmonary capillary wedge pressure (10). Subtypes of PAH (10) were identified by focused history, physical examination, and applicable laboratory or imaging investigations. All patients underwent complete blood count, electrolyte analysis, renal function tests, liver enzyme and function tests, hepatitis serology, and serology for CTDs and vasculitides. For imaging studies, all patients underwent contrast-enhanced computed tomography angiography. Additional tests, such as HIV serology and ventilation-perfusion scans, were performed as required. Patients were followed in clinic every three months by a specialized nurse clinician and a respiratory physician specializing in pulmonary hypertension care. More frequent visits were indicated for acute illnesses or changes in management. Less frequent visits were arranged for patients with significant travel distances. At each scheduled visit, patients underwent pulmonary function tests (spirometry, lung volumes and diffusing capacity), 6MWD, and standardized assessment of WHO functional class by the nurse clinician or physician. In addition, current medications, any complications and clinical signs of right heart failure were documented at every visit. All data were entered into a computerized database program.

From July 2001 to June 2005, patients with PAH, including IPAH, familial and associated with CTD, congenital systemic to pulmonary shunts, portal hypertension, HIV, drugs or toxins were assessed for therapy. Treatment with monotherapy was initiated for patients with WHO class II (unless 6MWD >600 m), III or IV disease who met the hemodynamic criteria for diagnosis of PAH. Bosentan was initiated for patients in WHO class II or III at a dose of 62.5 mg twice daily and titrated to a dose of 125 mg twice daily, unless the patient had liver enzyme abnormalities. Liver enzyme levels were measured weekly for the first eight weeks of therapy and every month thereafter. For patients who were unable to tolerate bosentan, monotherapy with sildenafil 25 mg three times daily was initiated. Patients with WHO class IV symptoms were considered for intravenous (IV) epoprostenol. Candidates for IV prostanoid therapy were cognitively and mechanically able to manage complex IV drug administration; within close proximity to medical care; and had no medical contraindications to prostanoid therapy (hypersensitivity to drug, severe left ventricular dysfunction). Calcium channel blockers (CCBs) were not started as

specific monotherapy for PAH, although patients using CCBs for digital ulcers or who had been started before referral had the option to continue them provided they remained clinically stable.

In July 2005, a treatment strategy based on a target 6MWD was adopted at the centre. 6MWD was chosen as the target variable due to patient acceptability, availability and prognostic significance in PAH (11). A target 6MWD of 350 m was chosen with consideration of the following:

1. Poorer prognosis in PAH with 6MWD <332 m (12); and
2. Improved survival in IPAH patients with 6MWD >380 m after three months of IV epoprostenol (13).

Patients with WHO class I disease were followed regularly without initiation of specific therapy. For patients with WHO class II, III or IV disease, bosentan monotherapy was initiated at 62.5 mg twice daily dosing, with a target dose of 125 mg twice daily irrespective of 6MWD. Bosentan monotherapy was continued if 6MWD remained >350 m and the medication was tolerated. If 6MWD dropped below 350 m on two successive follow-up appointments, sildenafil was added at 25 mg three times daily. If 6MWD dropped below 350 m or failed to improve to >350 m on two further successive follow-up appointments despite combination therapy with bosentan and sildenafil, IV epoprostenol or subcutaneous treprostinil were considered. Candidacy for IV/subcutaneous therapies is described above. For patients treated with epoprostenol or treprostinil, the medication was added to their oral treatment regimen unless the patient was unable to tolerate all three medications due to hypotension or liver enzyme abnormalities. In patients who were not candidates for prostanoid therapy, bosentan and sildenafil were continued. Patients who were potential candidates for lung transplantation were referred for transplantation assessment. No patients from the first treatment were included in the second period.

Patient groups were compared using the unpaired Student's *t* test. Survival (all cause mortality) was plotted on a Kaplan-Meier survival curve. Survival was calculated using a log-rank test adjusted for covariances of age, WHO class, 6MWD, right atrial pressure, mean pulmonary artery pressure, cardiac output, cardiac index, pulmonary vascular resistance and PAH subtype.

RESULTS

Between 2001 and 2005, 34 patients with PAH were diagnosed and followed in the clinic. Mean values and SDs are presented. Five patients were men with a mean age of 53.3±15.3 years, and 29 patients were women with a mean age of 48.9±18.4 years. Subtypes of PAH in this patient cohort were 13 IPAH, 16 CTD-PAH and five other (Table 1). The mean WHO functional class at treatment initiation was 2.9±0.9. Patients who were not started on treatment had their WHO functional class at initial assessment recorded. The distribution of WHO functional class was three patients in class I, five in class II, 16 in class III and nine in class IV. The mean 6MWD at initial presentation was 321±118 m. Of the 34 patients, 28 were treated with bosentan monotherapy and six patients were observed conservatively (including patients treated with CCB alone) because of WHO functional class I status or WHO functional class II status and high 6MWD. Of the patients in WHO functional class IV, none qualified for IV epoprostenol because of inability to manage the treatment at home and lack of adequate social support. Although lung transplantation was discussed with all patients younger than 65 years of age who remained in WHO class III or IV despite therapy, no patients were referred for lung transplantation during this time period. At the end of the observation period, 26 patients were on bosentan monotherapy, one patient was on sildenafil, five were on bosentan and CCB, and two WHO class I patients were either observed or taking CCBs.

From 2001 to 2005, there was a statistically significant reduction (ie, improvement) in mean WHO functional class at six months (2.5±0.8; *P*<0.015), nine months (2.5±0.8; *P*<0.005) and 12 months (2.5±0.9; *P*<0.03) of therapy compared with the patients' baseline functional class (at treatment initiation) (Figure 1). There was also a

TABLE 1
Baseline patient demographics, parameters and pulmonary arterial hypertension subtypes

	Period	
	2001–2005 (n=34)	2005–2009 (n=60)
Age at initial assessment, years	50.4±16.9	56.5±16.7
Age, years (females)	48.9±18.4	53.7±16.8
Age, years (males)	53.3±15.3	60.6±16.3
Female sex, %	85.3	71.6
Male sex, %	14.7	28.3
WHO class at treatment initiation	2.9±0.9	2.8±0.7
6-min walk distance at treatment initiation, m	321±118	354±117
Right atrial pressure, mmHg	9±5	12±6
Pulmonary artery pressure, mmHg	48±15	45±12
Cardiac output, L/min	4.7±2.2	5.0±1.7
Cardiac index, L/min/m ²	2.6±1.1	2.7 ±0.9
Pulmonary vascular resistance, Wood units	9.1±6.3	6.5±4.7
Pulmonary arterial hypertension subtypes, n (%)		
Idiopathic	13 (38.3)	25 (41.7)
Familial	1 (2.9)	0 (0)
Collagen vascular disease	16 (47.1)	21 (35.0)
Congenital systemic to pulmonary shunts	2 (5.9)	9 (15.0)
Portal hypertension	0 (0)	2 (3.3)
Anorexigen exposure	0 (0)	2 (3.3)
Pulmonary veno-occlusive disease	1 (2.9)	1 (1.7)
Persistent pulmonary hypertension of the newborn	1 (2.9)	1 (1.7)

Data presented as mean ± SD unless otherwise indicated

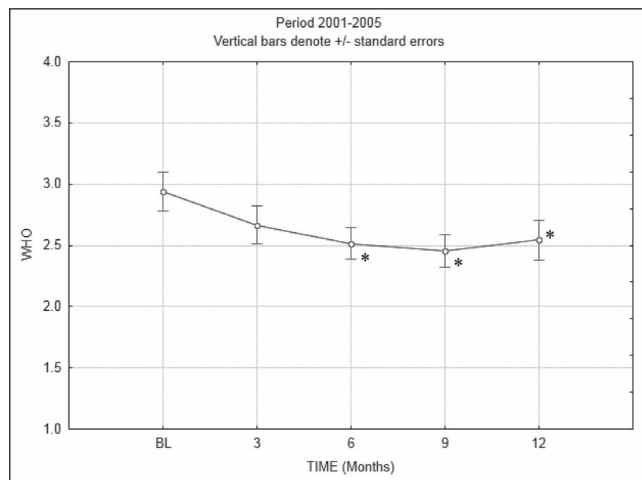


Figure 1 Mean WHO class in patients treated before the initiation of 6 min walk distance-directed therapy. *Statistically significant difference compared with baseline (BL). WHO WHO functional classification

statistically significant increase in mean 6MWD at three months (383±113 m; $P<0.005$), six months (401±102 m; $P<0.006$), nine months (400±109 m; $P<0.001$) and 12 months of therapy (399±110 m) ($P<0.004$) compared with baseline (321±118 m) (Figure 2). The survival rate in this era, before initiation of the 6MWD goal-directed strategy, was 95% at one and two years. Two patients died during the study period, one related to PAH and one of unknown etiology (Figure 3).

Between July 2005 and July 2009, 60 patients with PAH (43 female and 17 male) were diagnosed and followed in the clinic. Subtypes included 25 IPAH, 21 CTD and 14 other causes (Table 1). The mean WHO functional class at treatment initiation was 2.8±0.7. The

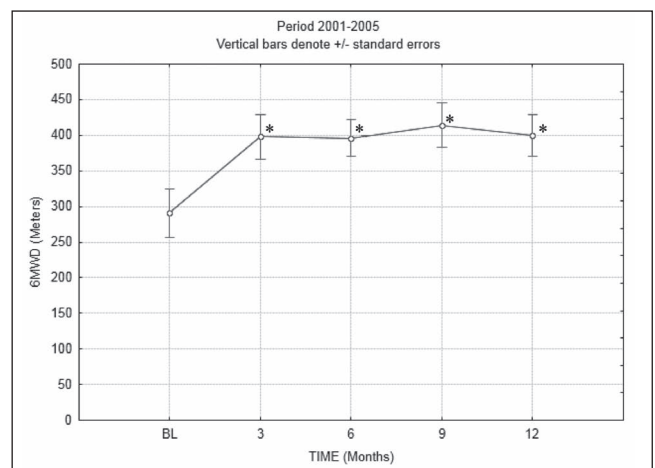


Figure 2 Mean 6 min walk distance (6MWD) in patients treated before the initiation of 6MWD-directed therapy. *Statistically significant difference compared with baseline (BL)

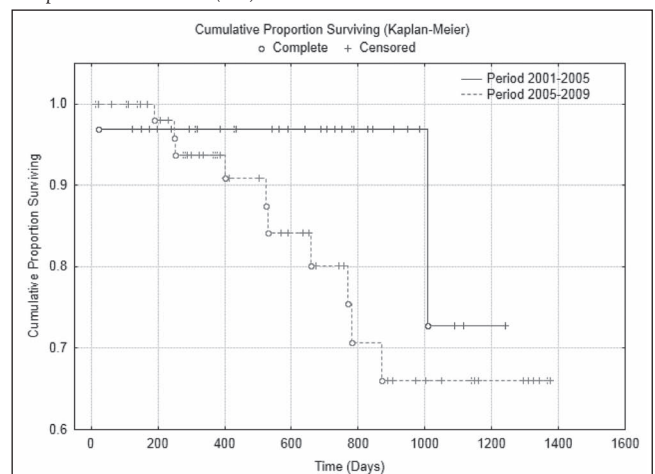


Figure 3 Kaplan-Meier survival curve before (2001 to 2005) and after (2005 to 2009) introduction of a 6 min walk distance-directed therapy strategy

distribution of WHO functional class was four patients in class I, nine in class II, 37 in class III and eight in class IV. The mean 6MWD at treatment initiation was 354±117 m. The majority of patients were initiated on treatment as per the target 6MWD strategy; however, there were some exceptions. Of the 60 patients, 51 were initiated on treatment with bosentan monotherapy according to protocol, one with sildenafil monotherapy (treatment was initiated before referral to the pulmonary hypertension clinic) and eight patients were observed conservatively because of WHO class I symptoms, WHO class II symptoms with high 6MWD or continued on CCB alone. At the end of the observation period, 40 patients were on bosentan monotherapy, seven were on sildenafil, 11 were on combinations of bosentan and sildenafil, and two were either observed with WHO class I symptoms or treated with CCBs. IV epoprostenol therapy was attempted in two patients but discontinued within two weeks due to severe headaches and hypotension. During this period, four patients were referred for lung transplantation. Three patients were listed for transplantation and one requested to be put on hold. By the end of the second phase of the study, the two listed patients remained active on the lung transplant waiting list. Of the eight patients with WHO class IV symptoms, all either declined IV prostanoid therapy or were not candidates.

During the period July 2005 to February 2009, 10 patients died, including one patient within days of starting treatment (six related to PAH, one not related and three unknown). One- and two-year survival rates were 95% and 80%, respectively. Patients lost to follow-up were presumed dead (worst case scenario) (Figure 3).

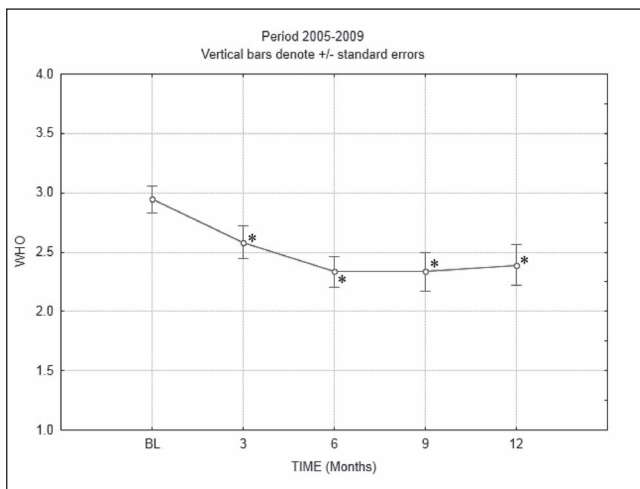


Figure 4) Mean WHO class in patients treated according to target 6 min walk distance (6MWD) treatment strategy. *Statistically significant difference compared with baseline (BL). WHO WHO functional classification

There was a statistically significant improvement in mean WHO functional class at three months (2.6 ± 0.8 ; $P < 0.05$), six months (2.3 ± 0.9 ; $P < 0.0001$), nine months (2.3 ± 0.9 ; $P < 0.0001$) and 12 months of therapy (2.3 ± 1.0 ; $P < 0.0005$) compared with baseline (2.8 ± 0.7) (Figure 4). At treatment initiation, the mean 6MWD was 354 ± 117 m. There was a statistically significant improvement in 6MWD at six months of therapy (381 ± 126 m [$P < 0.05$]), followed by a decline in 6MWD, reaching a mean 6MWD similar to baseline mean 6MWD (Figure 5).

Comparing patients in the earlier treatment era with those in the target 6MWD therapy group revealed no statistically significant differences with respect to age, initial WHO functional class, initial 6MWD or baseline hemodynamic parameters (right atrial pressure, mean pulmonary artery pressure, cardiac output, cardiac index, pulmonary vascular resistance) (Table 1).

DISCUSSION

Examining the registry data from our pulmonary hypertension clinic, pre- and postadoption of a 6MWD target-directed treatment strategy showed no improvement in one- or two-year survival rate using this strategy compared with standard PAH monotherapy. The second era, although not statistically different, had worse survival in the first two years of follow-up. Both treatment eras had better survival rates compared with historical controls, despite no patients being treated with IV prostanoids. There was an improvement in 6MWD by six months of therapy in both groups compared with baseline, which was maintained at 12 months in the earlier cohort, but not in the target 6MWD treatment group. For WHO functional class, there was an improvement by six months of therapy in both groups, which was maintained at 12 months in both groups. The overall conclusion from the present observational study is that there were no notable differences in survival, 6MWD or WHO functional class when this simple strategy to escalate PAH therapies was applied.

There are a number of possible confounders and limitations to these 'real-life' data. Small study size and lack of randomization limited the strength of the statistical analysis. The inclusion of patients with various causes of PAH may have also introduced bias into the study because most therapeutic research has involved patients with IPAH. Although selecting only IPAH patients would be more statistically robust, it may not reflect the 'real-life' practice we aimed for in the present study. This is also true for patients with medical comorbidities who we did not exclude but may have introduced bias. This may account for the nonstatistically significant lower survival rate apparent in the first 200 days in the second patient cohort.

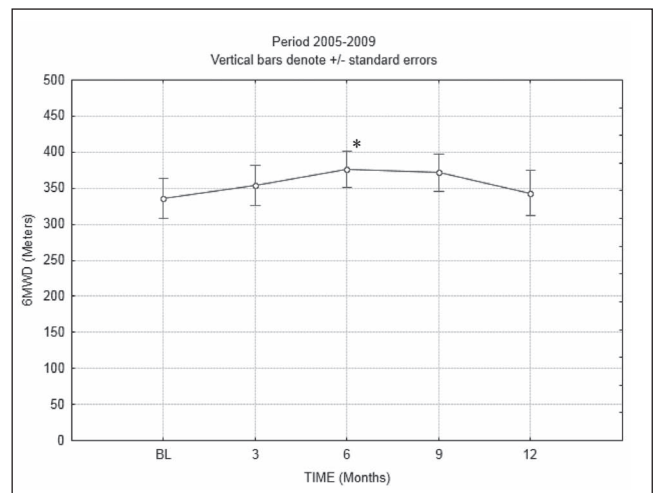


Figure 5) Mean 6 min walk distance (6MWD) in patients treated according to target 6 MWD treatment strategy. *Statistically significant difference compared with baseline (BL)

The 6MWD strategy itself may be the reason there was no improvement in survival compared with standard PAH monotherapy. It is possible that the 6MWD strategy allowed patients to deteriorate too much before escalating therapy. Although we considered the available prognostic information of the 6MWD test and published values in other studies, the 6MWD value used in the present study was not the same as other studies published since. Perhaps a different absolute 6MWD, or distance corrected for age, height and sex would have been more efficacious. Furthermore, by using this strategy, a large proportion of the patients remained on monotherapy; therefore, these data may not sufficiently reflect patient outcomes on combinations of medications. Using a single target variable may not be sufficient for making treatment decisions in these complex patients, and guidelines for pulmonary hypertension management now emphasize the importance of following multiple parameters in PAH (14).

The present study adds to the current literature by providing a real-life example of a PAH treatment strategy. Our clinic aimed to study the effectiveness of a simple, widely available clinical target (ie, 6MWD) in making PAH treatment decisions. We are continually assessing this real-life cohort's clinical status and responses to treatment, with the ongoing goal of developing an effective treatment protocol that is acceptable to patients.

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