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Maximal Exercise Testing Using the Incremental Shuttle Walking Test Can Be Used to Risk Stratify Patients with Pulmonary Arterial Hypertension

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Abstract

Rationale: Exercise capacity predicts mortality in pulmonary arterial hypertension but limited data exist on the routine use of maximal exercise testing.

Objectives: This study evaluates a simple to perform maximal test, the incremental shuttle walking test, and its utility in risk stratification in pulmonary arterial hypertension (PAH).

Methods: Consecutive patients with pulmonary hypertension were identified from the ASPIRE registry (2001-2018). Thresholds for levels of risk were identified at baseline, tested at follow-up and incorporation into current risk stratification approaches assessed.

Results: Of 4524 treatment-naïve patients with pulmonary hypertension who underwent maximal exercise testing 1,847 patients had PAH. A step-wise reduction in one-year-mortality was seen between levels 1 (≤30m; 32% mortality) and 7 (340-420m; 1% mortality) with no mortality for levels 8-12 (≥430m) in idiopathic and connective tissue disease related PAH. Thresholds derived at baseline of ≤180m (>10%; high-risk), 190-330m (5-10%; intermediate-risk) and ≥340m (<5%; low-risk of one-year mortality) were applied at follow-up and also accurately identified levels of risk. Thresholds were incorporated into the REVEAL 2.0 risk score calculator and French low-risk approach to risk stratification and distinct categories of risk remained.

Conclusion: We have demonstrated that maximal exercise testing in PAH stratifies mortality-risk at baseline and follow-up. This study highlights the potential value of the incremental shuttle walking test as an alternative to the 6-minute-walk-test, combining some of the advantages of maximal exercise testing whilst maintaining the simplicity of a simple to perform field test.

Pulmonary arterial hypertension (PAH) is a life-shortening condition and risk stratification is recommended to guide treatment decisions. Exercise limitation is an early presenting symptom in PAH and measures of exercise capacity are typically severely reduced (1, 2). Exercise testing is recommended as part of a multi-parameter assessment in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) and REVEAL 2.0 risk scores, and has been frequently used as an end-point in clinical trials (3, 4).

The six-minute walking test (6MWT) is the most widely used exercise test in pulmonary hypertension, and is inexpensive and simple to perform (5, 6). Absolute 6MWT distance (6MWD) correlates with haemodynamic parameters in idiopathic pulmonary arterial hypertension (IPAH) and predicts survival at baseline and follow-up (7-10). Nonetheless there are concerns about a ceiling effect above a distance of 450m, and younger patients with severe disease may walk beyond 500m (11-14). In addition, improvement of 6MWD in response to treatment has not been found to be independently prognostic in PAH (13, 15). Cardiopulmonary exercise testing (CPET) is a maximal test and provides comprehensive evaluation of multi-organ response to physical effort. Parameters from CPET are associated with prognosis in PAH but its utility in routine clinical practice may be limited by cost, complexity and duration of procedure (16).

The incremental shuttle walking test (ISWT) is an alternative maximal test for assessing patients with PAH, and is used in other forms of cardiac and respiratory disease (17-19). Previous studies have demonstrated correlation between ISWT distance (ISWD) and haemodynamic parameters at right heart catheterisation (RHC), and have confirmed that baseline and follow-up distances predict survival in PAH (20). The ISWT has potential

advantages over the 6MWT in that it does not suffer from a ceiling effect, potentially allowing better assessment in patients who are younger or have less severe disease (20, 21). Given these recognised limitations of the 6MWT, we sought to evaluate whether the ISWT could be used to risk stratify patients with PAH. The aim of this study was to assess whether thresholds could be identified for the ISWT and implemented into widely-used risk stratification scores.

Methods

Patients were identified from the ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry, diagnosed with pulmonary hypertension between 1st February 2001 and 31st May 2018. Patients underwent multi-modality assessment as previously described (22). Data were collected prospectively and patients were required to have an ISWT performed at time of PH diagnosis, prior to commencement of PAH therapy. Patients with idiopathic, drug and heritable PAH were grouped and referred to hereafter as IPAH. Patients with IPAH and PAH related to connective tissue disease (PAH-CTD) typically represent the majority of patients with PAH in registry studies and patients in these groups were therefore used to establish and test thresholds (23-25). Thresholds for low, intermediate and high-risk of one-year mortality were defined as <5%, 5-10% and >10%, respectively, and were identified in incident, treatment-naïve patients based on one-year mortality (or need for lung transplantation) for each level. Thresholds were evaluated at follow-up, defined as the first reassessment beyond 90 days after commencing treatment. For the 6MWT it is recognised that younger patients with severe disease may walk low-risk distances of >500m, therefore in the

present study a sensitivity analysis was performed on patients aged <50 to assess whether the thresholds remained valid in stratifying risk in younger patients (12, 26).

Incremental Shuttle Walking Test

The ISWT was undertaken as described by Singh *et al* (27), and as part of the standard patient evaluation. Patients complete a 10m length keeping in time to an external audible signal. Level one consists of 3 lengths (30m) and each subsequent level adds one extra length to the preceding level. The initial speed is a slow walk, 0.50m/s, increasing incrementally every level to a maximum of 2.37m/s at level 12. Each level takes one minute to complete and the test finishes at the end of level 12, a distance of 1020m. The patient continues until they are too breathless or unable to keep up with the required pace (see table 2 for details of walking speeds). Patients who were unable to perform an ISWT due to breathlessness were ascribed an ISWT distance of 0m.

Mortality Data

Mortality data were obtained from the nationally-reported NHS Personal Demographics Service, updated when a death is registered in the UK, and transplant data were obtained from local databases. Patients who emigrated (n=3) were excluded from the study, as were patients not linked to a record on the Personal Demographics Service (n=2). The outcome assessed was transplant-free survival and census date was 31st May 2019, providing at least one-year of follow-up for all patients.

Statistical Analysis

Statistical analysis was performed using SPSS v25 (IBM, Chicago) and GraphPad Prism v8.

Continuous data were displayed as either mean ±SD or median (first quartile, third quartile) for

non-parametric data. Demographics were compared using paired and unpaired T-test for

parametric data, and Wilcoxon signed-rank and Mann-Whitney U-tests for non-parametric

data. Frequencies were compared using X^2. A p value of <0.05 was considered significant.

Kaplan-Meier survival curves were compared using log rank X^2. From receiver operating

characteristic (ROC) analysis, a c-statistic was produced to compare variations on risk scores.

Where ISWT levels demonstrated one-year mortality of 0%, these levels were combined for

Kaplan Meier analysis and correlation with haemodynamics.

Ethics

Approval by the relevant ethics committee was sought and gained (STH14169, NHS Research

Ethics Committee 16/YH/0352), and written consent was waived.

Results

A total of 4524 treatment-naïve patients with pulmonary hypertension, who had undergone

ISWT at the time of diagnosis, were identified from the ASPIRE registry. Baseline characteristics

for different forms of pulmonary hypertension are displayed in online data supplement Table

E1. Of these, 1240 had either IPAH or PAH-CTD; table 1. Kaplan Meier analysis for ISWD in all

forms of PH and for IPAH/PAH-CTD at baseline are displayed in figure 1.

IPAH and PAH-CTD

Incident, treatment naive patients with IPAH (n=603) had significant disease at right heart

catheterisation, with a median mPAP 52mmHg, pulmonary vascular resistance (PVR) 10.5 WU

and cardiac index 2.2 l/min/m^2. Patients with PAH-CTD (n=637) had a median mPAP 43mmHg,

PVR 7.3 WU and cardiac index 2.6 l/min/m^2. The majority of patients received either

combination oral treatment or treatment including a prostanoid.

Within one-year of diagnosis, 197 patients (15.4%) with IPAH and PAH-CTD had died or

undergone transplantation. Levels of the ISWT demonstrated an inverse relationship with risk

of one-year mortality (Table 2). Patients who walked 0-30m had a one-year mortality of 32%. A

step-wise reduction in percentage-mortality was seen at each level until a distance of ≥430m

where there was a 0% mortality. Assignment of risk categories required concordance for both

IPAH and PAH-CTD (Table 2). A high-risk of one-year mortality (>10%) was therefore defined as

a distance of ≤180m, low-risk (<5%) as an ISWD ≥340m and intermediate-risk 190-330m.

Corresponding values for cardiac MRI and pulmonary haemodynamic parameters are displayed

in table 3. A stepwise reduction in right ventricular end-systolic volume index (%predicted) was

seen with each level of the ISWT. When comparing baseline haemodynamic parameters

between patients completing level 1 (≤30m) and level 2 (40-70m) of the ISWT, there were

significant differences in mean right atrial pressure, cardiac index and mixed venous oxygen

saturation (*p* all <0.05).

At follow-up ISWT the thresholds accurately identified patients at low, intermediate and

high-risk in the combined IPAH and PAH-CTD cohort (one-year survival 97%, 94%, 78%,

respectively), and in the individual disease groups. Kaplan Meier graphs showing five-year

transplant-free survival at baseline, follow-up and demonstrating risk transition are displayed in figure 2.

Age <50 Years

Using the above thresholds in incident patients aged <50, 30% were identified as low-risk and had 0% one-year mortality. Seventy patients (28%) were intermediate risk where observed one-year mortality was lower than expected at 3%, whereas 42% of patients were high-risk and had a one-year mortality of 15%. A scatterplot showing baseline and follow-up distances and one-year mortality is shown in the online data supplement (Figure E1).

Treatment Response

Baseline median ISWD was 110m (40, 220) and paired tests at follow-up were available for 879 patients. At follow-up, 132 (15%) patients had improved their ISWT risk-category (i.e. had improved to either intermediate or low-risk distance) and 83 (9%) had deteriorated. A scatterplot demonstrating individual baseline and follow-up distance is displayed in Figure 3. At paired testing, a median improvement of +10m (-30, +50; $p<0.0001$) was seen overall. Patients who achieved at least one ISWT level higher than at baseline (n=329, 37%), and therefore achieved a higher velocity, had significantly better 1 and 5-year survival (90% and 54%, respectively) than those who either remained in the same level (n=314, 36%; 1 and 5-year survival 84% and 37%; $p<0.0001$) or deteriorated (n=236, 27%; 1 and 5-year survival 79% and 36%; $p<0.0001$), while there was no significant survival difference between those who were stable or deteriorated ($p=0.61$; figure 2).

Use in Conjunction with Risk Stratification Scores

Patients with baseline RHC data available including mean right atrial pressure (mRAP) and cardiac index (n=1076) were selected to assess whether ISWD thresholds could be used in conjunction with other risk stratification scores, in place of 6MWD thresholds. For the FPHR low-risk invasive approach to the ESC/ERS guidelines, a low-risk 6MWD of >440m was substituted with a low-risk ISWD of ≥340m. Survival differed significantly based on the number of low-risk criteria (0-4) between all groups (*p*<0.05) and at ROC analysis produced a c-statistic of 0.61 (95% CI 0.57-0.66), which was unchanged when used in the IPAH group in isolation, and higher than when the FPHR approach was used without any walking test (c-statistic 0.59; 95% CI 0.55-0.64). Kaplan Meier analysis for an abbreviated three-category risk score (3 or 4 criteria = low-risk, 1 or 2 criteria = intermediate-risk, 0 criteria = high-risk) is displayed in figure 4a, demonstrating separation of curves for each risk category (*p* all <0.0001). Using this three-category FPHR risk score, low and high-risk groups were accurately identified (one-year survival 96% and 78%, respectively) but risk in the intermediate group was underestimated (one-year survival 87%).

When assessing the REVEAL 2.0 score in the same population, three variations for substituting 6MWD with ISWD were derived based on i) thresholds similar to the 6MWD thresholds used in REVEAL 2.0; ii) thresholds of low, intermediate and-high risk identified at baseline; and iii) thresholds of low, intermediate and-high risk identified at baseline with an extra point addition or deduction for very-high (≤30m) and very-low risk (≥430m), respectively, derived from baseline data shown in table 2. The REVEAL 2.0 c-statistic for one-year mortality without a walking test was 0.66 (95% CI 0.62-0.70); including ISWD thresholds from variation iii

produced a c-statistic of 0.71 (95% CI 0.67-0.75), compared to 0.69 for variations i and ii. Low

(≤6), intermediate (7-8) and high-risk (≥9) REVEAL 2.0 scores (scores grouped as previously

described (28)) accurately predicted one-year mortality; survival curves are displayed in Figure

4, and detailed analysis of one-year mortality for REVEAL 2.0 scores are displayed in Figure 5. In

all variations, patients with a REVEAL 2.0 score ≤6 had a 0% one-year mortality, and patients

with a REVEAL 2.0 score of ≥9 had a one-year mortality of 19-20%.

Discussion

In a large cohort of patients with IPAH and PAH-CTD we have demonstrated that routine use of

maximal exercise testing can risk stratify patients into low, intermediate and-high risk of one-

year mortality/lung transplantation. Using a three-level risk score we have identified ISWT

thresholds at baseline, shown the clinical utility in conjunction with other risks stratification

scores and demonstrated that thresholds identified at baseline risk-stratify patients at follow-

up.

Exercise capacity is recognised as an important physiological marker in PAH, and as a

validated measure, the 6MWT has been the mainstay of exercise testing in PAH both in routine

practice and in clinical trials (9). In early studies assessing PAH therapies, 6MWD was

demonstrated to be a marker of treatment response (29). Absolute distances are prognostic,

and deterioration of 6MWD is strongly associated with poor prognosis (15, 30). Despite this

there has been criticism of the 6MWT, particularly over its role as an endpoint in clinical trials

(13, 31), as prospective and retrospective studies have been unable to demonstrate that

improvements in 6MWD are independently associated with survival (15, 30). Furthermore, it is a submaximal test and may suffer from a ceiling effect, potentially limiting its use in younger patients or those with mild disease (32).

We have previously shown that, as an alternative but maximal field walking test, the ISWT provides a measure of maximal exercise capacity without a ceiling effect and can identify exercise limitation in asymptomatic patients diagnosed with pulmonary hypertension in WHO FC I (20, 33). Using data from the present study we have now identified that maximal exercise testing using the ISWT can risk-stratify patients with IPAH and PAH-CTD. At baseline, in incident and treatment naïve patients, levels of the ISWT demonstrated good separation for both one-year and longer-term survival. As a risk stratification tool, thresholds established at baseline were applicable at follow-up. As has been demonstrated with other prognostic investigations and risk stratification tools, patients who improved their risk profile demonstrated comparable longer-term survival to patients originally displaying that level of risk (24, 34, 35).

A drawback of the 6MWT is that it suffers from a ceiling effect, whereby patients who walk >450m at baseline may not improve their walking distance in response to treatment despite improvements in WHO functional class and haemodynamics (20). In this study we have shown that, even amongst patients who walked ≥340m at baseline and remained in the low-risk group at follow-up, 63% improved absolute ISWD in response to treatment. At higher follow-up distances of ≥430m and ≥530m, 68% and 69% of patients, respectively, were able to improve their ISWD after commencing treatment. A further criticism of the 6MWT is that younger patients with severe PAH, and therefore at high-risk of mortality, may still be able to walk distances >500m (12). We have therefore undertaken an exploratory analysis on patients

aged <50 and identified no mortality at one year for patients with a low-risk ISWT distance of ≥340m.

We have also demonstrated that patients who were able to achieve a higher ISWT level had significantly better long-term survival than patients who either remained in the same level or achieved a lower level at follow-up. This is expected as each level of the ISWT requires a higher maximal walking or running velocity, which has been shown to correlate with maximal oxygen intake (peak VO_2) in other cardiorespiratory diseases (18, 19, 36). Peak VO_2 has been identified as a strongly prognostic marker of survival in PAH when measured by incremental CPET (37), and other centres have confirmed the value of incremental exercise testing in the assessment of patients with pulmonary hypertension (38).

Associations between incremental exercise testing and haemodynamics have been shown previously, and we have expanded upon this by showing association between this incremental test and important prognostic parameters from cardiac MRI with a stepwise reduction in right ventricular end-systolic volume %predicted with each level of the ISWT (20, 35, 38).

Our data demonstrate that ISWT thresholds can now be considered for incorporation into widely-used risk stratification tools. Using the French low-risk invasive approach to risk stratification, substitution of the 6MWT distances with equivalent distances for low, intermediate and high-risk from the ISWT continued to show five distinct risk groups at survival analysis. When combined into a three-category risk score, patients at low (3 or 4 criteria) and high-risk (0 criteria) had a one-year mortality of 4% and 22%, respectively. Boucly et al. noted the difficulties of defining an intermediate-risk group and we found that the presence of one or

two low-risk criteria underestimated one-year mortality, which was also seen when this approach was applied to the REVEAL population (25, 28). The c-statistic of 0.61 in our population of patients with IPAH is similar to that identified when the French approach was tested in the REVEAL registry (0.62), although no c-statistic is provided in the original research (25, 28).

In the REVEAL 2.0 risk score we have shown that when 6MWT distances are substituted with variations of ISWT thresholds, a three-level risk score accurately predicts one-year mortality in this population. The c-statistic of 0.71 is lower than that identified in REVEAL 2.0 (0.76), and this may be the result of a phenotypically-different PAH population. In our study we included only patients with IPAH and PAH-CTD rather than other forms of PAH such as congenital heart disease (CHD). Furthermore, in our study, risk stratification approaches were applied to treatment-naïve patients rather than a mixture of incident and prevalent patients as in the REVEAL study. These factors, and particularly the absence of patients with PAH-CHD (the presence of which scores -2 points in REVEAL 2.0) may also explain why a relatively small number of our patients were identified as being at low-risk by REVEAL 2.0 when compared to the original study and external validation studies (28, 39).

Limitations

Distances achieved at 6MWT and ISWT are not directly comparable, and the thresholds used in this study were identified from baseline data. While we have assessed and confirmed that these thresholds remain valid at follow-up, as in any single-centre study both the thresholds and their role in risk stratification tools require prospective validation in a separate population. Although

we are unable to directly compare sensitivity and specificity for 6MWT and ISWT thresholds in the same population, our data support the use of the ISWT as a tool in risk stratification in PAH. In this study we have focused on patients with IPAH and PAH-CTD and further work is required to assess whether these thresholds remain valid in patients with other forms of PAH. All-cause mortality or transplantation was used as the primary end-point, and patients may have died from causes unrelated to PAH. Follow-up data were unavailable for 29% of patients, although a proportion of these patients did not survive to follow-up (15.4% died within one year of diagnosis). These missing data do not include patients who attended clinic but were unable to perform the ISWT due to breathlessness as these patients were assigned a distance of 0m. Finally, while the thresholds identified a large proportion of patients at high-risk of one-year mortality, this may reflect a high-risk population as demonstrated by the large number of patients with a high REVEAL 2.0 score with a corresponding one-year mortality of around 20%. The ISWT is simple to perform, and in contrast to the 6MWT requires a 10m rather than 30 m corridor, with an average time to complete the test of around 3 minutes, making it straightforward to incorporate into clinical practice.

Conclusion

Maximal exercise testing can be used to risk stratify patients with pulmonary hypertension including IPAH and PAH-CTD, and this study supports the routine use of maximal exercise testing in conjunction with other risk stratification tools. This study highlights the potential value of the incremental shuttle walking test as an alternative to the 6-minute-walk-test,

combining some of the advantages of maximal exercise testing whilst maintaining the simplicity

of a simple to perform field test.

References

1. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. American journal of respiratory and critical care medicine. 2006;173(9):1023-30.

2. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104(4):429-35.

3. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 2015;46(4):903.

4. Demir R, Kucukoglu MS. Six-minute walk test in pulmonary arterial hypertension. Anatol J Cardiol. 2015;15(3):249-54.

5. Sciurba FC, Slivka WA. Six-minute walk testing. Seminars in Respiratory and Critical Care Medicine. 1998;19(4):383-92.

6. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. American journal of respiratory and critical care medicine. 2002;166(1):111-7.

7. Provencher S, Chemla D, Herve P, Sitbon O, Humbert M, Simonneau G. Heart rate responses during the 6-minute walk test in pulmonary arterial hypertension. Eur Respir J. 2006;27(1):114-20.

8. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, Spreeuwenberg MD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. Medicine and science in sports and exercise. 2008;40(10):1725-32.

9. 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(2):156-63.

10. 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(2):164-72.

11. 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(25 Suppl):D73-81.

12. Vachiery JL, Yerly P, Huez S. How to detect disease progression in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2012;21(123):40-7.

13. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. European respiratory review : an official journal of the European Respiratory Society. 2013;22(130):487-94.

14. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, et al. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. Vascul Pharmacol. 2005;43(1):36-9.

15. 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(4):780-8.

16. Weatherald J, Farina S, Bruno N, Laveneziana P. Cardiopulmonary Exercise Testing in Pulmonary Hypertension. Ann Am Thorac Soc. 2017;14(Supplement_1):S84-S92.

17. Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. Breathe (Sheff). 2015;11(2):128-39.

18. Morales FJ, Montemayor T, Martinez A. Shuttle versus six-minute walk test in the prediction of outcome in chronic heart failure. Int J Cardiol. 2000;76(2-3):101-5.

19. Lewis ME, Newall C, Townend JN, Hill SL, Bonser RS. Incremental shuttle walk test in the assessment of patients for heart transplantation. Heart (British Cardiac Society). 2001;86(2):183-7.

20. Billings CG, Hurdman JA, Condliffe R, Elliot CA, Smith IA, Austin M, et al. Incremental shuttle walk test distance and autonomic dysfunction predict survival in pulmonary arterial hypertension. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2017;36(8):871-9.

21. Billings CG, Lewis R, Hurdman JA, Condliffe R, Elliot CA, Thompson AAR, et al. The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. Pulm Circ. 2019;9(2):2045894019848649.

22. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J. 2012;39(4):945-55.

23. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012;142(2):448-56.

24. Kylhammar D, Kjellstrom B, Hjalmarsson C, Jansson K, Nisell M, Soderberg S, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J. 2018;39(47):4175-81.

25. Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017;50(2):1700889.

26. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. American journal of respiratory and critical care medicine. 2012;186(8):790-6.

27. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47(12):1019-24.

28. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019;156(2):323-37.

29. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med. 1990;112(7):485-91.

30. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2015;34(3):362-8.

31. Rubin LJ. The 6-minute walk test in pulmonary arterial hypertension: how far is enough? American journal of respiratory and critical care medicine. 2012;186(5):396-7.

32. Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". Chest. 2010;137(6):1258-60.

33. Billings CG, Lewis R, Armstrong IJ, Hurdman JA, Smith IA, Austin M, et al. Incremental Shuttle Walking Test Distance Is Reduced in Patients With Pulmonary Hypertension in World Health Organisation Functional Class I. Front Med (Lausanne). 2018;5:172.

34. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50(2):1700740.

35. Lewis RA, Johns CS, Cogliano M, Capener D, Tubman E, Elliot CA, et al. Identification of Cardiac Magnetic Resonance Imaging Thresholds for Risk Stratification in Pulmonary Arterial Hypertension. American journal of respiratory and critical care medicine. 2020;201(4):458-68.

36. Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test. a systematic review. Chest. 2014;145(6):1357-69.

37. 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(4):1193-8.

38. Shah SJ, Thenappan T, Rich S, Sur J, Archer SL, Gomberg-Maitland M. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. Circ Heart Fail. 2009;2(4):278-86.

39. Anderson JJ, Lau EM, Lavender M, Benza R, Celermajer DS, Collins N, et al. Retrospective Validation of the REVEAL 2.0 Risk Score With the Australian and New Zealand Pulmonary Hypertension Registry Cohort. Chest. 2020;157(1):162-72.

Table 1: Baseline demographics in patients with IPAH and PAH-CTD

	IPAH & PAH CTD	IPAH	PAH-CTD
n=	1240	603	637
Female (%)	71	61	80
Age	64 (53, 72)	62 (47, 72)	66 (57, 73)
WHO FC I (%)	0	0	0
WHO FC II (%)	13	13	13
WHO FC III (%)	63	59	67
WHO FC IV (%)	23	27	19
BMI (kg/m^2)	27 (23, 31)	28 (24, 33)	26 (22, 30)
mRAP (mmHg)	9 (6, 14)	11 (7, 15)	8 (5, 12)
mPAP (mmHg)	48 (40, 56)	52 (46, 60)	43 (34, 51)
PAWP (mmHg)	10 (8, 13)	11 (8, 13)	10 (7, 12)
PVR (WU)	9.1 (5.7, 13.2)	10.5 (7.8, 14.5)	7.3 (4.7, 11.7)
SvO2 %	63 (56, 69)	61 (55, 67)	65 (58, 71)
Cardiac Output (l/min)	4.3 (3.2, 5.1)	4.0 (3.2, 5.0)	4.4 (3.4, 5.3)
Cardiac Index (l/min/m^2)	2.4 (1.9, 2.9)	2.2 (1.8, 2.7)	2.6 (2.0, 3.1)
ISWD (m)	110 (40-220)	120 (40-260)	100 (40-195)
Treatment (%)			
None or CCB	2	3	1
Oral mono	33	27	38
Combo oral	42	43	41
Prostanoid +/- oral	23	27	20

Continuous data were non-parametric and are presented as median (1st quartile, 3rd quartile).

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension related to connective tissue disease; WHO FC = World Health Organisation Functional Class; BMI = body mass index; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; SvO2 = mixed venous oxygen saturations; ISWD = incremental shuttle walking test distance; CCB = calcium channel blockers.

Table 2: Levels of the incremental shuttle walking test and associated mortality

ISWT Level*	Distance	Speed (m/s)	n (%)	one-year mortality (%)		
			IPAH & PAH-CTD	IPAH & PAH-CTD	IPAH	PAH-CTD
Level 1	0-30m	0.50	267 (22)	31.8	23.4	40.8
Level 2	40-70m	0.67	206 (17)	18.5	11.0	24.3
Level 3	80-120m	0.84	196 (16)	15.3	12.4	17.8
Level 4	130-180m	1.01	172 (14)	14.5	15.2	14.2
Level 5	190-250m	1.18	137 (11)	9.5	4.5	14.1
Level 6	260-330m	1.35	110 (9)	4.5	5.5	3.6
Level 7	340-420m	1.52	69 (6)	1.4	2.3	0
Level 8	430-520m	1.69	52 (4)	0	0	0
Level 9	530-630m	1.86	18 (2)	0	0	0
Level 10	640-750m	2.03	9 (1)	0	0	0
Level 11	760-880m	2.20	2 (0)	0	0	-
Level 12	890-1020m	2.37	2 (0)	0	0	-

*Each level has a duration of one minute. Abbreviations: ISWT = incremental shuttle walking test; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension related to connective tissue disease; ISWD = incremental shuttle walking distance.

Table 3: Association between ISWT level and haemodynamic and cardiac MRI parameters

ISWT level	n	WHO FC	mRAP (mmHg)	CI (l/min/m^2)	SvO2 (%)	RVEF (%)	RVESVi (%pred)
1	267	3.6 ±0.5	12 (8,16)	2.04 (1.67, 2.65)	58 (52, 66)	33 (27-42)	283 (225, 405)
2	206	3.3 ±0.5	10 (6, 15)	2.31 (1.80, 2.86)	61 (54, 67)	32 (25-44)	277 (163, 338)
3	196	3.1 ±0.5	10 (6, 14)	2.28 (1.81, 2.90)	62 (55, 69)	35 (24, 48)	253 (159, 371)
4	172	3.0 ±0.4	9 (6, 13)	2.40 (1.89, 2.9)	64 (58, 68)	35 (28, 43)	240 (162, 328)
5	137	2.9 ±0.5	8 (6, 13)	2.50 (2.00, 3.05)	66 (59. 70)	34 (25, 44)	237 (152, 328)
6	110	2.7 ±0.5	8 (5, 11)	2.60 (2.17, 3.20)	68 (63, 71)	36 (25, 48)	176 (132, 264)
7	69	2.6 ±0.5	9 (6, 12)	2.56 (2.20, 3.17)	66 (59, 71)	42 (34, 50)	183 (122, 258)
8-12	83	2.4 ±0.5	7 (5, 9)	2.85 (2.22, 3.22)	69 (63, 72)	40 (27, 48)	159 (120, 241)

Data are displayed as mean ±SD or median (first quartile, third quartile)

Abbreviations: ISWT = incremental shuttle walking test; MRI = magnetic resonance imaging; WHO FC = World Health Organisation Functional Class; mRAP = mean right atrial pressure; CI = cardiac index; SvO2 = mixed venous oxygen saturations; RVEF = right ventricular ejection fraction; RVESVi %pred = right ventricular end systolic volume, indexed for body surface area and corrected for age and sex.

Figure Legends:

Figure 1: Kaplan Meier survival curves for a) ISWD in all PH; b) ISWD in IPAH and PAH-CTD. Abbreviations: ISWT = incremental shuttle walking test; ISWD = ISWT distance; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; LHD = left heart disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension due to connective tissue disease

Figure 2: Kaplan Meier survival curves for a) ISWD risk groups at baseline; b) transition of ISWD risk groups between baseline and follow-up; c) comparison of patients who, at follow-up, achieved at-least one higher ISWT level, achieved the same ISWT level, or achieved a lower level than at baseline. Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance

Figure 3: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD in patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease (n=879). Abbreviations: ISWD = incremental shuttle walking test distance

Figure 4: Kaplan Meier analysis demonstrating survival in: a) FPHR low-risk approach; b) REVEAL 2.0 variation i (ISWD 0-180m = +1; 190-330 = 0; 340-420 = -1; ≥430m = -2 points); c) REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; ≥340 = -1 point); d) REVEAL 2.0 variation iii (ISWD

0-30 = +2; 40-180 = +1; 190=330 = 0, 340-420 = -1; ≥430m = -2 points). Abbreviations: REVEAL =

Registry to Evaluate Early and Long-Term PAH Disease Management, FPHR = French Pulmonary

Hypertension Registry, ISWD = incremental shuttle walking test distance

Figure 5: Risk of mortality by REVEAL 2.0 score, using variations of REVEAL 2.0 incorporating

ISWD as follows: REVEAL 2.0 variation I (ISWD 0-180m = +1; 190-330 = 0; 340-420 = -1; ≥430m =

-2 points); REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; 340-420 = -1 point);

REVEAL 2.0 variation iii (ISWD 0-30 = +2; 40-180 = +1; 190=330 = 0, 340-420 = -1; ≥430m = -2

points). Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease

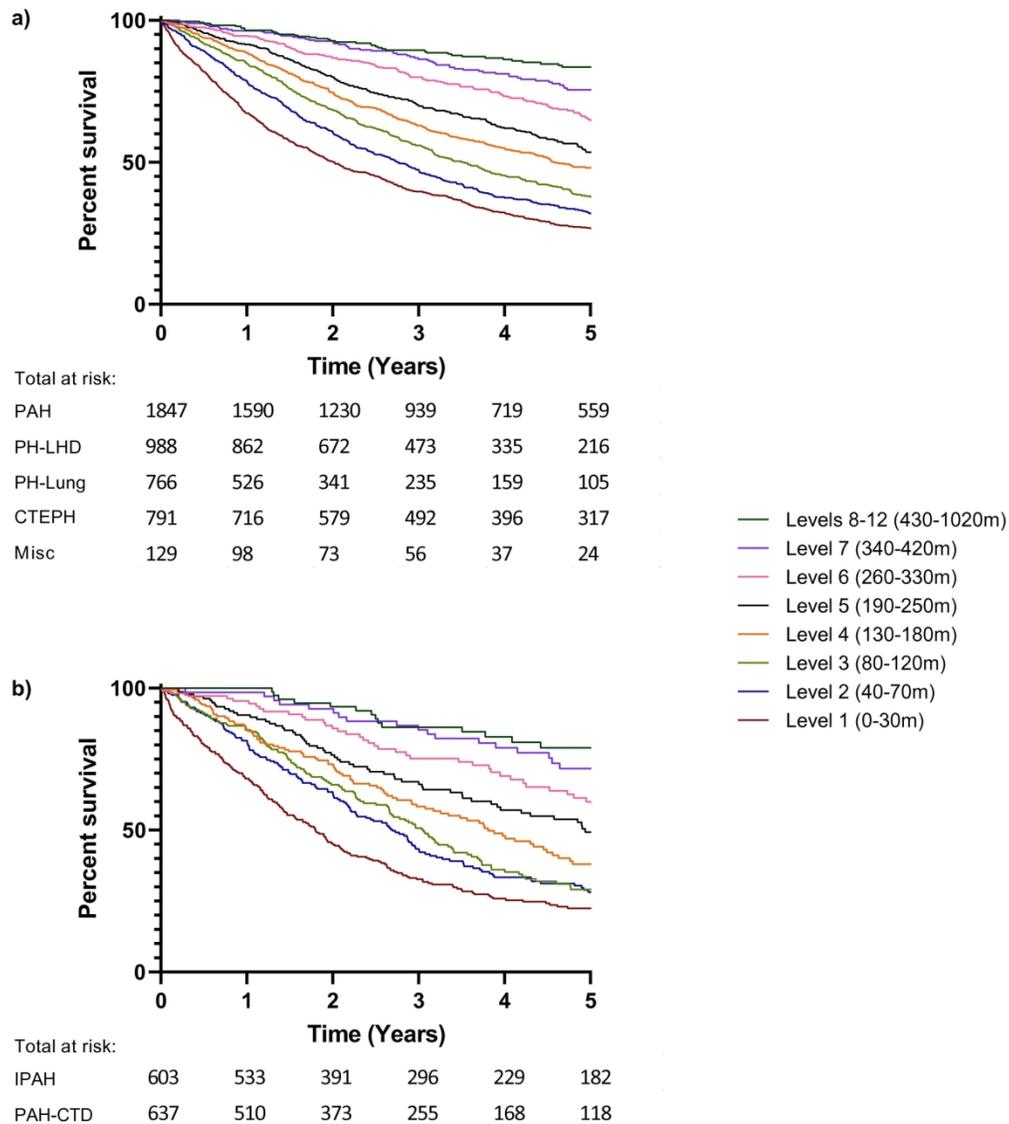Management; ISWD = incremental shuttle walking test distance

Figure 1: Kaplan Meier survival curves for a) ISWD in all PH; b) ISWD in IPAH and PAH-CTD
Abbreviations:
ISWT = incremental shuttle walking test; ISWD = ISWT distance; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; LHD = left heart disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension due to connective tissue disease
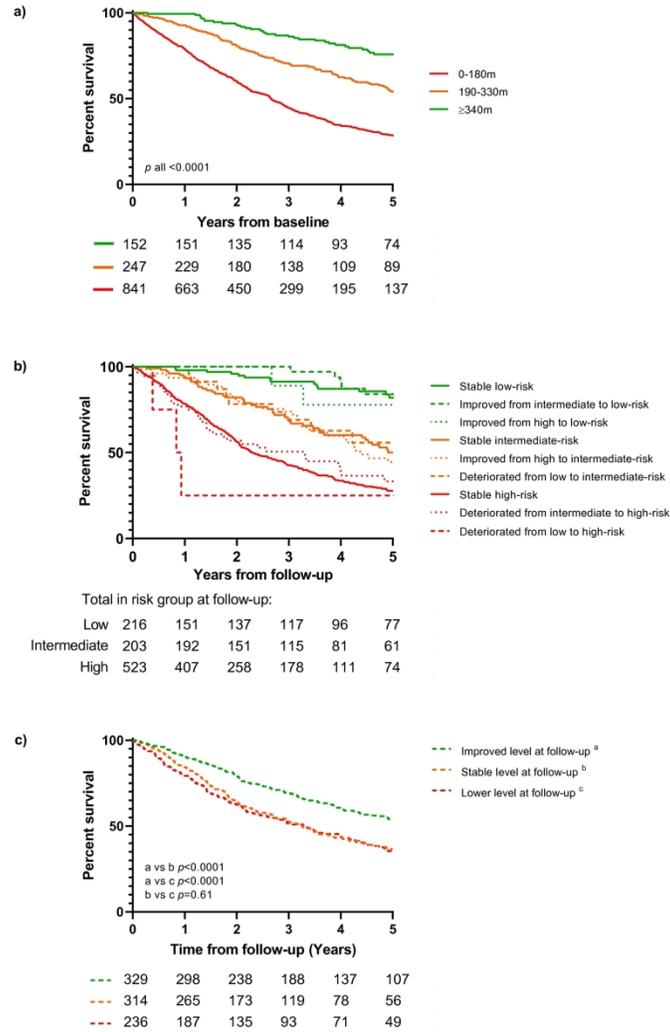
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Figure 2: Kaplan Meier survival curves for a) ISWD risk groups at baseline; b) transition of ISWD risk groups between baseline and follow-up; c) comparison of patients who, at follow-up, achieved at-least one higher ISWT level, achieved the same ISWT level, or achieved a lower level than at baseline.
Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance

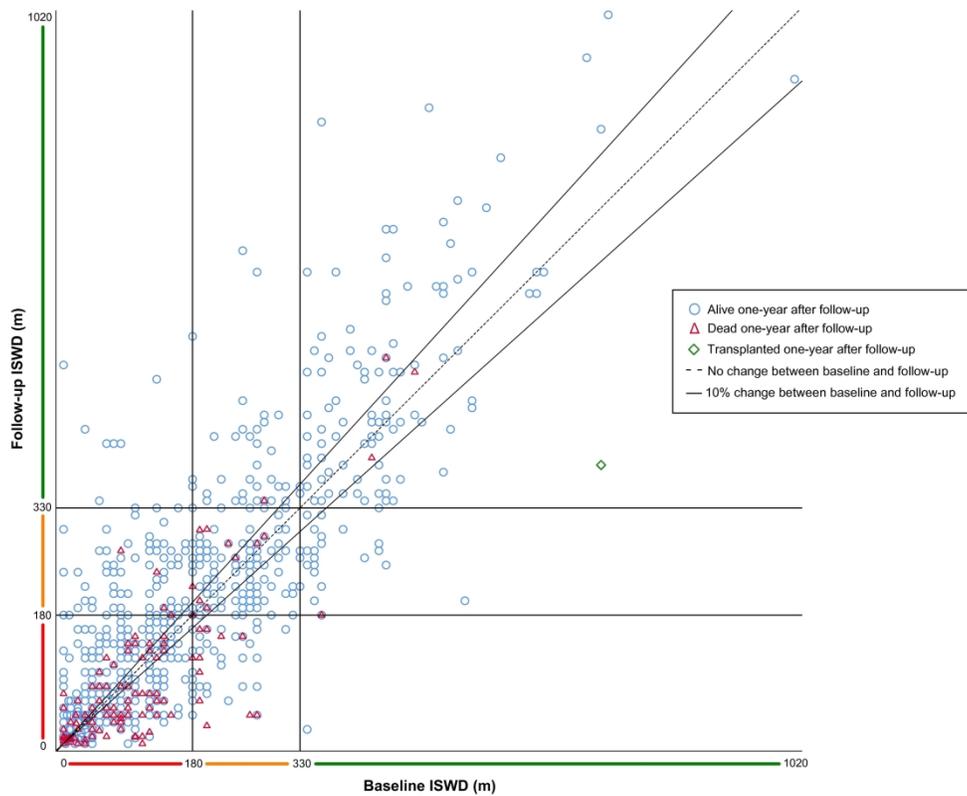209x296mm (300 x 300 DPI)

Figure 3:   A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD in patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease (n=879).
Abbreviations: ISWD = incremental shuttle walking test distance
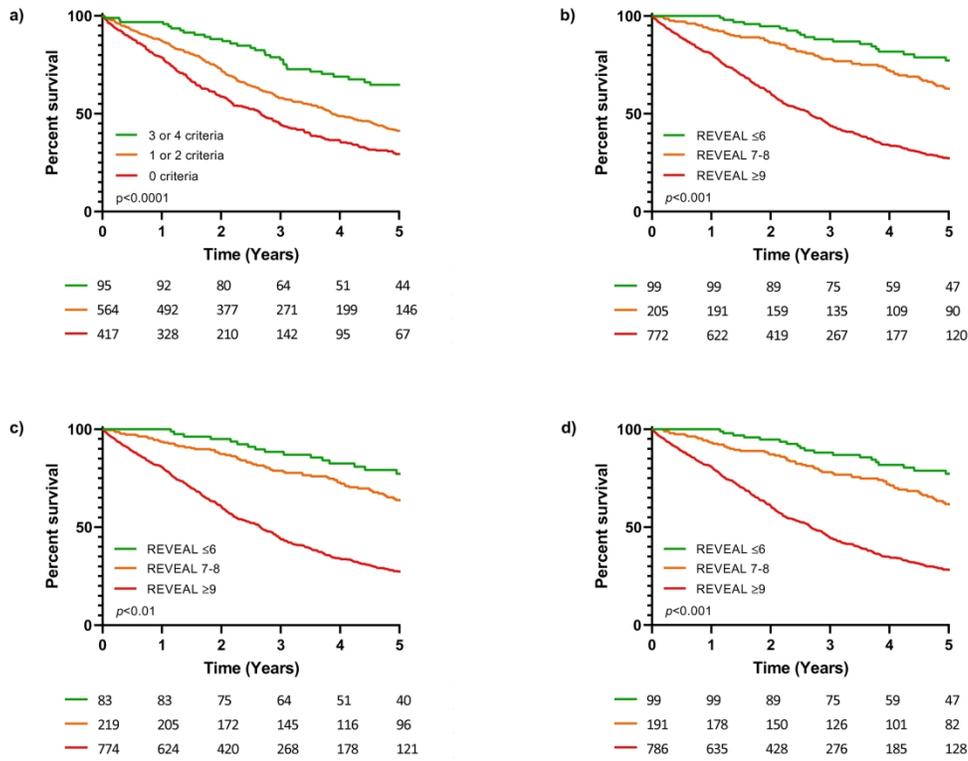
253x221mm (300 x 300 DPI)

Figure 4: Kaplan Meier analysis demonstrating survival in:
a) FPHR low-risk approach;
b) REVEAL 2.0 variation i (ISWD 0-180m = +1; 190-330 = 0; 340-420 = -1; ≥430m = -2 points);
c) REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; ≥340 = -1 point);
d) REVEAL 2.0 variation iii (ISWD 0-30 = +2; 40-180 = +1; 190=330 = 0, 340-420 = -1; ≥430m = -2 points)
Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management, FPHR = French Pulmonary Hypertension Registry, ISWD = incremental shuttle walking test distance

232x181mm (300 x 300 DPI)

	Variation i		Variation ii		Variation iii	
	n (%)	1y mortality (%)	n (%)	1y mortality (%)	n (%)	1y mortality (%)
REVEAL ≤6	99 (9)	0	83 (8)	0	99 (9)	0
REVEAL 7	65 (6)	3	70 (7)	3	64 (6)	3
REVEAL 8	140 (13)	9	149 (14)	8	127 (12)	9
REVEAL 9	174 (16)	12	175 (16)	12	166 (15)	11
REVEAL 10	225 (21)	18	226 (21)	18	186 (17)	15
REVEAL 11	161 (15)	19	161 (15)	19	174 (16)	18
REVEAL ≥12	212 (20)	28	212 (20)	27	260 (24)	29

Figure 5: Risk of mortality by REVEAL 2.0 score, using variations of REVEAL 2.0 incorporating ISWD as follows:
REVEAL 2.0 variation I (ISWD 0-180m = +1; 190-330 = 0; 340-420 = -1; ≥430m = -2 points);
REVEAL 2.0 variation ii (ISWD 0-180m = +1; 190-330m = 0; 340-420 = -1 point);
REVEAL 2.0 variation iii (ISWD 0-30 = +2; 40-180 = +1; 190=330 = 0, 340-420 = -1; ≥430m = -2 points)
Abbreviations: REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; ISWD = incremental shuttle walking test distance

108x28mm (300 x 300 DPI)

Online Data Supplement

Maximal Exercise Testing Using the Incremental Shuttle Walking Test Can Be Used to Risk Stratify Patients with Pulmonary Arterial Hypertension

Robert A. Lewis MBChB; Catherine G. Billings PhD; Judith A. Hurdman MD; Ian A. Smith MSc; Matthew Austin MSc; Iain J. Armstrong PhD; Jennifer Middleton MBChB; Alexander M.K Rothman MBChB, PhD; John Harrington; Neil Hamilton DPharm; Abdul G. Hameed PhD; A.A. Roger Thompson PhD; Athanasios Charalampopoulos MD; Charlie A. Elliot MD; Allan Lawrie PhD; Ian Sabroe PhD; Jim M. Wild PhD; Andrew J. Swift PhD; Robin Condliffe MD; David G. Kiely MD

Table E1: Baseline demographics in all forms of pulmonary hypertension

	All PH	PAH	PH-LHD	PH-Lung	CTEPH	Group 5
n=	4524	1847	988	766	791	129
Female (%)	61	69	66	46	50	60
Age	67 (56, 75)	63 (49, 71)	74 (67, 78)	68 (62, 75)	65 (53, 74)	62 (50, 70)
WHO FC I (%)	1	1	1	0	1	3
WHO FC II (%)	19	18	24	12	22	10
WHO FC III (%)	62	63	66	55	64	63
WHO FC IV (%)	18	19	9	33	13	23
BMI	28 (24, 33)	27 (23, 32)	30 (26, 35)	27 (24, 33)	28 (25, 33)	26 (22, 32)
mRAP (mmHg)	10 (7, 15)	9 (6, 14)	14 (11, 18)	9 (6, 13)	10 (7, 14)	10 (6, 14)
mPAP (mmHg)	44 (35, 52)	47 (37, 55)	38 (32, 46)	41 (33, 49)	46 (37, 53)	45 (35, 52)
PAWP (mmHg)	12 (9, 17)	11 (8, 14)	22 (19, 26)	12 (9, 15)	12 (9, 14)	12 (9, 14)
PVR (WU)	6.2 (3.5, 10.3)	8.0 (4.8, 12.0)	3.0 (2.1, 4.7)	5.7 (3.4, 9.2)	7.3 (4.4, 11.1)	6.8 (4.3, 9.8)
SvO2 %	65 (58, 70)	65 (57, 71)	66 (60, 70)	66 (60, 71)	62 (57, 68)	63 (56, 71)
Cardiac Output (l/min)	4.6 (3.6, 5.9)	4.5 (3.4, 5.6)	5.0 (4.1, 6.1)	5.0 (3.8, 6.4)	4.5 (3.5, 5.7)	4.7 (3.9, 6.2)
Cardiac Index (l/min/m²)	2.6 (2.0, 3.1)	2.5 (1.9, 3.2)	2.7 (2.3, 3.2)	2.7 (2.1, 3.4)	2.3 (1.9, 2.8)	2.7 (2.1, 3.3)
ISWD (m)	120 (40, 220)	130 (50, 250)	120 (40, 200)	80 (30, 150)	160 (60, 290)	90 (40, 195)
Treatment (%)						
None or CCB	40	8	96	65	19	28
Oral monotherapy	34	38	4	29	68	38
Combo oral	17	36	0	5	7	23
Prostanoid +/- oral	9	18	0	2	5	12

Continuous data were non-parametric and are presented as median (1st quartile, 3rd quartile). Abbreviations: PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; PH-LHD = pulmonary hypertension due to left heart disease; PH-Lung = pulmonary hypertension due to lung disease; CTEPH = chronic thromboembolic pulmonary hypertension; WHO FC = World Health Organisation Functional Class; BMI = body mass index; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; SvO2 = mixed venous oxygen saturations; ISWD = incremental shuttle walking test distance; CCB = calcium channel blocker

Figure E1: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD in patients aged <50 with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease

Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance
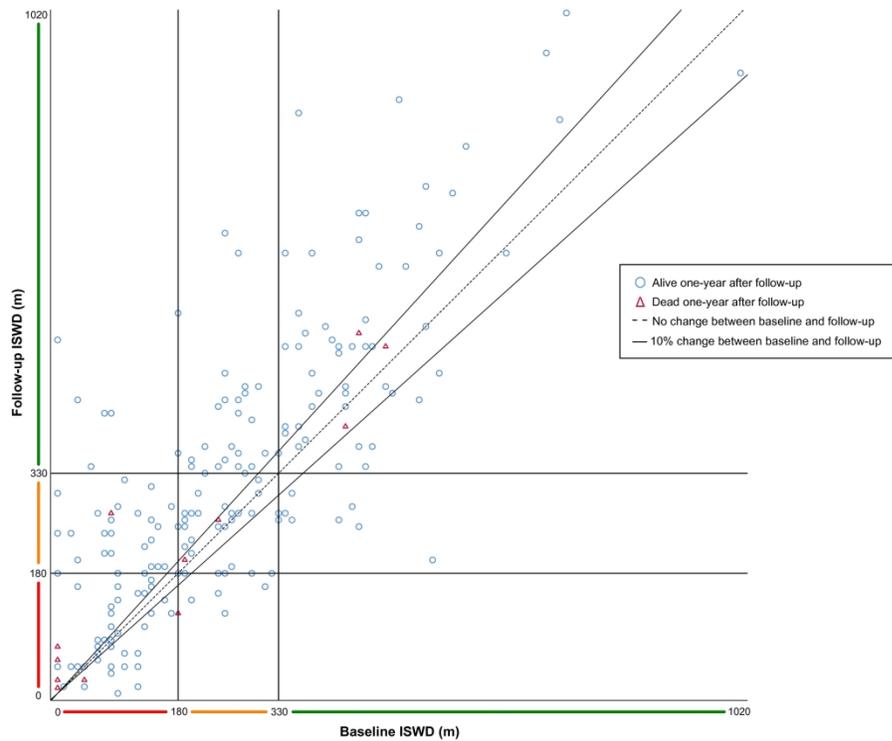
Figure E1: A scatterplot showing individual baseline and follow-up ISWT distances, and mortality or transplant within one-year of follow-up ISWD in patients aged <50 with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension due to connective tissue disease
Abbreviations: ISWT = incremental shuttle walking test, ISWD = incremental shuttle walking test distance

274x211mm (300 x 300 DPI)