Remote evaluation of risk and physiological response to therapeutic escalation and clinical worsening in patients with pulmonary hypertension

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Abstract (348)

Background

International guidelines for the treatment of patients with pulmonary arterial hypertension (PAH) recommend the use of risk stratification to optimise therapy to achieve and maintain a low-risk profile. However, recommended methods require hospital-based investigations. We sought to develop a method for daily, remote risk evaluation.

Methods

Consecutive patients (n=5820) with pulmonary hypertension (PH) were identified from the ASPIRE registry and stepwise Cox regression applied to identify parameters associated with survival. A physiological risk score was applied to all patients and survival assessed by the Kaplan-Meier method. Physical activity was measured in patients with PAH implanted with insertable cardiac monitors (ICM, n=80) to provide a remote measure of exercise capacity. In patients with PAH and implanted pulmonary artery pressure (PAP) monitor and ICM (n=28) we undertook a time-stratified bidirectional case–crossover study to determine the physiology of therapeutic escalation (TE) and clinical worsening and a remote physiological risk score applied to the data.

Results

Age, male sex, PH aetiology, WHO functional class (FC), incremental shuttle walk-distance (ISWD), heart rate reserve (HRR) and total pulmonary resistance (TPR) as independent predictors of survival. Mortality increased with each decile of baseline physiological risk ($p<0.001$). In patients with PAH, thresholds of physiological risk were used to classify patients into low-, intermediate-low-, intermediate-high-, and high-risk groups for one-year mortality, which were well matched to COMPERA-2.0 score-stratified groups (Cohen's weighted Kappa 0.61). ICM-measured physical activity decreased with indicators of increased clinical risk (WHO-FC, NT-proBNP, ISWD, COMPERA-2.0, $p<0.0001$). Following TE, remote monitored mean PAP and TPR were reduced, and cardiac output (CO) and physical activity increased at days seven, four, 22 and 42 respectively ($p<0.05$). Clinical worsening events (CWE) were preceded by an increased remote monitored mean PAP and TPR and reduced CO and physical activity ($p<0.05$). Change in remote physiological risk score identifiable six days after TE and twelve days prior to a CWE ($p<0.05$).

Conclusion

Remote risk evaluation may facilitate personalised medicine and proactive management. The physiological risk score accurately stratifies patients with PH and may be applied to remote monitoring data for early evaluation of clinical efficacy and detection of clinical worsening.

Introduction:

Pulmonary arterial hypertension (PAH) is a life-shortening condition driven by remodelling and constriction of pulmonary arterioles that leads to increased pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP), and right heart failure.[1] Without treatment the median survival is less than 3 years.[2] Licensed therapies target vasoconstriction and vasodilatation of the pulmonary vasculature[3] and increase 5-year survival to ~60%.[4–6] Combination oral therapy, upfront dual[7] or sequential combination therapy,[8,9] are superior to oral monotherapy. However, not all patients respond to therapy,[10] side effects are common[8,9] and current assessment of therapeutic efficacy requires hospital-based invasive and non-invasive testing.[11]

European guidelines provide an expert-opinion-based risk-stratification score to aid treatment decisions, categorising patients as low (<5%), intermediate-low (5–10%), intermediate-high (10-20%) or high (>20%) risk of 1-year mortality, which assess symptoms, exercise capacity, and right ventricular function.[11] Risk thresholds have been validated in three European registries.[12–15] Patients who improve to a low-risk profile at follow-up have superior outcomes compared to those who fail to demonstrate clinical improvement. Current clinical approaches aim to improve and maintain patients in the low-risk group[16] and as such, there is significant interest in the identification of remote measures that may offer early evaluation of clinical efficacy following treatment change or identify early clinical deterioration, enabling early therapeutic intervention and improved early phase clinical studies.

In a large registry of patients with pulmonary hypertension (PH) attending a PH referral centre, we sought to identify parameters with an established relationship to survival that may be monitored remotely.[17] We used these to develop a novel physiological risk score that accurately risk stratifies patients in a manner comparable to the COMPERA 2.0 model.[11] In an independent cohort of patients, with PAH and implantable PAP and insertable cardiac monitors (ICM), we undertook a time-stratified bidirectional case–crossover study[18] to evaluate changes in physiology and remote physiological risk score following clinically indicated therapeutic escalation (TE) and at the time of clinical worsening events (CWE). Our findings demonstrated that remote monitored physiology provides an effective means for early evaluation of clinical efficacy and clinical worsening in patients with PAH.

Methods:

Patient Population

De-identified clinical data were collected from consecutive patients from the ASPIRE registry (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre – research ethics approval number 22/EE/0011) database between February 2001 and May 2019.[17] All patients underwent systematic evaluation, including echocardiography, blood testing, exercise testing, lung function testing, multimodality imaging, and right heart catheterisation,[19] in accordance with nationally agreed and audited standards of care[20] (Table 1). Mortality data were obtained from the NHS Personal Demographics Service, for which electronic records are automatically updated when a death is registered in the United Kingdom. All patients on PAH therapies were followed up as part of the national service specification for patients with PH. No patients were lost to follow-up. Patients who had undergone lung transplantation were censored at the time of surgery; all other surviving patients were censored on 31st of May 2019.

Baseline Risk and Survival Analysis

Assessment of baseline risk was made using the 4-strata COMPERA 2.0 criteria and thresholds.[11,15] At baseline, before initiation of PAH therapy, each variable was graded from 1 to 4, and the mean was calculated by dividing the sum of all grades by the number of variables and rounding to the nearest integer with the following definitions: 1 = low, 2 = intermediate-low, 3 = intermediate-high, and 4 = high risk. Field walk test thresholds were modified to accommodate the incremental shuttle walk distance (ISWD) used in the ASPIRE registry: 1 = >330m, 2 = 330-260m, 3 = 250-190m, 4 = <180m.[21]

Physiological Risk Score

Within the ASPIRE cohort, parameters were assessed for relationship to survival using univariate Cox regression analysis with a *P* value of <0.05 considered statistically significant. Metrics that were statistically significant in univariate analysis with approved, assessable means of remote monitoring were entered into a stepwise, backward multivariate Cox regression model correcting for age, sex and WHO disease classification (table 2). Parameters with a multivariate *P* value of <0.05 were used for the development of a physiological risk score. The z-scores for age, resting heart rate, total pulmonary resistance (TPR) and ISWD were weighted by their hazard ratio and summed to generate a physiological risk score. Locally estimated scatterplot smoothing regression analysis (LOESS) was performed to identify risk thresholds for 1-year mortality of <5%, 5–10%, 10-20% and >20% for patients with PAH.

Physical Activity

To permit daily, remote evaluation of exercise capacity, the relationship between physical activity, indicators of clinical risk and field walk test was examined from 80 patients with ICMs (LinQ, Medtronic) implanted as part of the UK National Cohort Study of Idiopathic and Heritable Pulmonary Arterial Hypertension (13/EE/0203). The device uses an embedded single axis accelerometer to capture movement. A minute is considered active if a threshold is reached incorporating deflection number and magnitude. This method has proven responsive in capturing activities of daily living that have been found to correlate with clinical events in patients with heart failure and / or atrial fibrillation.[22–26]

Advanced haemodynamic and insertable cardiac monitoring

Patients with a confirmed diagnosis of PAH, in WHO functional class (FC) III were enrolled in **F**easibility of Novel Clinical Trial **I**nfrastructure, Design and **T**echnology for Early Phase Studies in Patients with **P**ulmonary **H**ypertension (FIT-PH, 19/YH/0354). A PAP monitor (CardioMems, Abbott) and ICM (LinQ, Medtronic) were implanted using standard techniques and remote monitoring data collected via regulatory approved online portals (Merlin, Abbott and CareLink, Medtronic). Clinical data including baseline demographics, treatment changes and CWEs were collected through FIT-PH and the ASPIRE registry and clinical events were reviewed by a multi-professional team. Cardiac output (CO) was calculated using a proprietary algorithm (Abbott) based on the PAP waveform, mean PAP, heart rate (HR), and a reference CO measured at implant. This has been tested against clinical right heart catheter data, demonstrating non-inferiority to clinically used CO measurement,[27,28] and utility in patients with PAH.[29]

Remote Physiological Risk Score

The z-scores for age, resting heart rate, total pulmonary resistance (TPR) and daily physical activity were weighted by hazard ratio and summed to generate a remote physiological risk score which was applied to daily remote monitored data.

Clinical management and events

A multi-professional team (respiratory physician, cardiologist, pharmacist, and specialist nurse) reviewed data, adjudicated events and directed treatment. Disease progression or worsening were defined as PAH-

related hospitalisation, escalation of disease-specific therapy or long-term oxygen therapy, or the need for lung transplantation as judged by the physician.[7,9] Disease progression was defined as a decrease from baseline of at least 15% in the incremental shuttle walk test accompanied by a worsening in WHO-FC.[7,9]

Waveform evaluation

Suspected artefactual PAP waveform readings were identified by a proprietary automatic algorithm or those two standard deviations (SD) above or below an individual patient's mean PAP. Manual review of suspect waveforms was undertaken to identify those resulting from non-rested physiological state, post walk-test, ventricular ectopic beats, transmission failure, incorrect frequency detection or damped waveforms. Following review by two qualified physicians, abnormal waveforms were excluded from statistical analysis (Supplemental Figure 1).

Statistical Analysis

Registry analysis: Continuous data are presented as mean ± standard deviation (SD), or as median and interquartile range (IQR) and categorical data as number and percentage. No imputations were made for missing data. Overall survival was evaluated using Kaplan-Meier analysis and log-rank test. Survival analyses were undertaken for the entire group and for subgroups of patients with PAH according to physiological risk at baseline. The associated hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Statistical analyses were performed using SPSS version 27 for MacOS.

Physical activity and remote monitoring analysis: A time-stratified bidirectional case–crossover approach was taken to provide remote monitoring data from the time of TE or CWE and matched control periods.[18] Therapeutic effect and clinical worsening data comprises periods of 90 and 60-days respectively where TE or a CWE occur at day 0 and the time window begins 30 days preceding the event. Control data comprises time periods of a matched duration not overlapping those sampled as TE or CWE periods (Supplemental Figure 2). Use of remote monitoring systems was evaluated by daily transmission adherence. The date of transmissions for each patient was analysed to estimate adherence to the request for daily data uploads. This metric was expressed as the number and percentage of days, or transmission, over the first 90-days. Data were tested for normality and statistical comparisons made using parametric and non-parametric methods as appropriate. Analysis of the effect of TE was undertaken comparing the 30-days preceding TE

with the 0-30- and 30-60-days following TE by one-way ANOVA with Dunnett's post-test correction for multiple testing. Analysis of the effect of CWE was undertaken comparing a baseline preceding TE (day -30 to -20) with the period of the CWE (day -5 to day 5) using a paired student's t-test. Time to effect was analysed using control and event data in a mixed effects model. Statistical analysis was performed using IBM SPSS version 26 and Prism 9 for macOS (version 9.3.0)

Research Ethics approval

Ethical approval was provided by NHS research ethics committees (ASPIRE:22/EE/0011; FIT-PH: 19/YH/0354; National Cohort Study of Idiopathic and Heritable Pulmonary Arterial Hypertension: 13/EE/0203).

Results:

Study Population and PAH Therapies

Between Feb 2001 and May 2019, 5820 consecutive patients with all forms of PH were identified from the ASPIRE Registry. Baseline demographics are presented in table 1. Median age was 63 ± 15.8 years. 127 (7.2%) of patients with PAH were treated with a calcium channel blocker and 644 (36.4%) were prescribed oral monotherapy, 646 (36.5%) dual-oral combination therapy and 354 (20.1%) prostanoid therapy either alone or in combination with oral therapy.

Baseline Variables Associated with Survival

Following baseline investigations there were 2923 mortality events. Significant predictors in univariate analysis were increasing age, male sex, PH pathogenesis, WHO-FC, ISWD, right atrial pressure, PAP, PVR, TPR, CO, systemic oxygen saturation and mixed venous oxygen saturation (table 2). Independent baseline predictors of death in multivariable Cox regression which are fixed and/or have the capacity to be monitored remotely were age, male sex, PH aetiology, WHO-FC, ISWD, heart rate and TPR (table 2).

Association of Baseline Physiological Risk Score with Survival in Patients with Pulmonary Hypertension

To develop a summary measure for early evaluation of therapeutic efficacy and/or clinical worsening, a physiological risk score was developed using the parameters identified employing multivariate Cox regression. Individual patient scores were calculated by summation of the z-score for age, resting heart rate, TPR, and physical activity weighted by hazard ratio. Each decile of baseline risk resulted in a reduction in survival at one, three and five years (Figure 1A, $p<0.001$ between group comparisons).

Association of Baseline Physiological Risk Score with Survival in Patients with Pulmonary Arterial Hypertension

At baseline 1771 patients with PAH were risk stratified using the 4-strata COMPERA 2.0 model. 157 (8.8%) patients were classified as low risk, 276 (15.6%) patients as intermediate-low risk, 683 (38.6%) patients as intermediate-high risk, and 655 (37.0%) as high risk. The Kaplan-Meier estimated survival rates one, three and five years after diagnosis for the low-risk group were 98%, 90% and 80%, respectively; for the intermediate-low risk group, 95%, 79% and 63%, respectively; for the intermediate-

high risk group, 88%, 63% and 44%, respectively; and for the high-risk group, 83%, 45% and 32%, respectively (Figure 1B, p<0.001 between group comparisons). At baseline, using LOESS-derived risk thresholds in a 4-strata physiological risk score, 91 (7.6%) patients were classified as low risk, 377 (32.8%) patients as intermediate-low risk, 564 (49.4%) patients as intermediate-high risk, and 116 (10.2%) as high risk. The Kaplan-Meier estimated survival rates one, three and five years after diagnosis for the low-risk group were 96%, 87% and 80%, respectively; for the intermediate-low risk group, 93%, 81% and 65%, respectively; for the intermediate-high risk group, 89%, 62% and 46%, respectively; and for the high-risk group, 83%, 45% and 28%, respectively (Figure 1C, p<0.001 between group comparisons). Risk stratification was constant between the 4-strata COMPERA 2.0 and 4-strata remote physiological risk score (Cohen's weighted Kappa 0.61).

Association of ICM-measured Physical Activity with Indicators of Clinical Risk

To facilitate daily, remote assessment, established discriminators of risk[11] were related to daily physical activity measured from an ICM (activities of daily living, Supplemental table 1, 2 and 3). Compared to patients with low-risk indicators, physical activity was reduced in those with intermediate and high-risk indicators for ISWD, WHO-FC, NT-proBNP and COMPERA 2.0 risk score (Figure 2, p<0.0001).

Physiological Response to Therapeutic Escalation and Clinical Worsening in Patients with Pulmonary Arterial Hypertension

To determine whether the identified parameters were stable over time and changed with clinical events, 28 patients with PAH were implanted with PAP monitors and ICMs, providing daily measurement of PAP, CO, heart rate and physical activity (Supplemental table 4, 5 and 6). There were no serious adverse events and two device-related adverse events (minor haemoptysis and ICM erosion, supplemental table 3 and 6). Following implantation, data completeness was 100% for ICM data and 91% for PAP monitor data. During follow-up 18 clinically indicated TEs and 13 CWEs were observed.

During periods without a TE or CWE physiological parameters and remote risk score were stable (Figure 3). Following routine review and clinician-directed increase in therapy ISWD, WHO-FC and NT-proBNP were improved with a mean time to assessment of 5.1 months (Figure 3A-D, p<0.05, Wilcoxon matched pairs). Consistent with identified improvements, remote monitored mean PAP and TPR were reduced and

an increase in CO and physical activity were seen compared to the 30-days preceding treatment change at days seven, four, 22 and 42 respectively (Figure 3E-J, $p<0.05$, one way ANOVA with Dunnett's correction).

To evaluate the changes related to disease worsening remote monitoring data was evaluated in the 30-days preceding and following CWEs (Figure 4). Following a CWE, ISWD, WHO functional class and NT-proBNP deteriorated (Figure 4A-D, $p<0.05$, Wilcoxon matched pairs). CWEs were preceded by an increase in remote monitored mean PAP and TPR as well as a reduction in CO and physical activity at least ten days prior to a CWE (Figure 4E-J, $p<0.05$, one way ANOVA with Dunnett's correction). In 8 patients changes were apparent at least 15-days prior to a CWE.

Application of Remote Physiological Risk Score to Remote Monitoring Data

To consolidate the multiple physiological signals provided by implanted devices into a single measure the z-score of TPR, resting heart rate and physical activity were weighted by hazard ratio and summed to provide a remote physiological risk score that was applied to remote monitoring data. Following a clinically indicated increase in therapy, a reduction in remote physiological risk score was identifiable at day six (Figure 5A) and preceding a CWE, a change in remote physiological risk score was identifiable at day -12 (Figure 5B).

Discussion:

Current guidelines for the diagnosis and management of patients with PAH recommend therapeutic optimisation to achieve and maintain a low-risk profile as a major treatment objective.[11] However, in clinical practice, a low risk profile is not achieved in most patients [12,14] and repeated risk assessment is infrequent. In patients with heart failure (not related to PAH), studies have shown that implanted devices provide daily measures of cardiovascular physiology that may be used for risk assessment, therapeutic optimisation, and service prioritisation.[30–34] In the present study, parameters independently associated with survival, that may be monitored remotely, were integrated to develop a physiological risk score for the assessment of patients with PH. In patients with PAH, a 4-strata remote risk score applied prior to initiation of therapy, identifies groups at low (<5%), intermediate-low (5-10%), intermediate-high (10-20%) and high (20%) risk of one year mortality, with significant differences in survival at 3 and 5 years.

Risk stratification after treatment initiation takes account of an individual patient's response to therapy and has been shown to provide better prognostic information.[35] However, the requirement for repeated in-hospital testing limits the capacity for iterative treatment changes designed to achieve and maintain a low-risk profile. To establish a means for remote, early, identification of clinical efficacy and/or clinical worsening, patients with PAH were implanted with two separate devices to collect data with known relationships to survival (a PAP monitor and ICM). There were no serious adverse events. In one patient mild haemoptysis was noted following implantation and in one patient an ICM was removed, and another ICM implanted due to erosion (supplemental table 7). One patient developed headaches and flushing related to the known interaction between selexipag and clopidogrel that increases selexipag levels;[36] symptoms resolved when clopidogrel was withdrawn and prasugrel initiated for the remainder of the 30-day post implantation period (supplemental table 7). Adherence with remote data collection in the 6-months following implantation was 100% for the ICM and 91% for the implanted PAP monitor. Following a clinically-indicated increase in therapy, change in remote monitored parameters were identifiable in advance of the 3–6-month period typical used in clinical studies and/or clinical practice to assess treatment response.[11] There were reductions in mean PAP and TPR and increases in CO and physical activity seen at day 7, 4, 22 and 42, compared to baseline, respectively. Additionally, all these parameters were altered 10 days prior to a CWE. When applied to remote monitoring data the developed remote physiological risk

score integrating remote monitoring data from the two separate devices accurately identified change in COMPERA 2.0 risk strata following a clinically indicated TE and, in the period, preceding a CWE.

All risk models provide a basic assessment of risk assessment; however the risk of an individual patient is impacted by other factors including age,[5,37] sex,[38] disease sub-group and disease trajectories.[39] Although more complex tools may be developed to more accurately evaluate risk, the primary limitation in their use is the frequency and location of assessment. The present study demonstrates that a risk score applied to remote monitored physiological data was sensitive to changes in disease-specific therapy and to clinical worsening. The capacity to assess risk more frequently, from a patient's home creates a feedback loop between the initiation of therapy and evaluation of clinical effect that has implications for both clinical practice and early phase clinical studies. Such an approach also has the potential to increase patient engagement and empower patients to invest further in their care and treatment. In addition, these methods may facilitate a personalised medicine approach whereby the efficacy of a new treatment strategy can be evaluated objectively, in real time, and optimised or withdrawn according to individual, patient-specific factors, risk status and side effects. Specifically, the ability to detect improvement and decompensation earlier facilitates timely intervention to achieve or maintain a low-risk status and where this is not possible the opportunity to consider alternative approaches. In a manner similar to that used in patients with heart failure,[30–34] remote, evaluation of risk, over a prolonged time, may also permit prioritisation of healthcare resources to those with declining risk status and/or guide the timing of TE, initiation of intravenous therapy and/or transplant. In clinical research, the increased frequency of haemodynamic and physical capacity evaluation may permit more complex study designs that are currently limited by the requirement for invasive/hospital-based investigations and provide valuable insight into individualised patient response, dose-response and time-to-effect.[40,41]

Limitations

Registry analysis

Registry analyses may be limited by lack of standardised visit schedules and missing values, however the number of patients in the registry is large and the centre adheres to nationally agreed and audited standards of care, ensuring that patients are carefully phenotyped, undergo regular follow-up and receive treatment in accordance with national policy and international guidelines. Nationalised mortality data

collections ensured no patient was lost to follow-up. All risk stratification was performed on data collected prior to the initiation of therapy thereby excluding important information related to the individual's response to therapy.

Remote monitoring

Haemodynamic and physical activity data was observed in the time preceding and following clinically indicated increases in therapy and CWEs. There was no placebo group and neither the patient nor the clinical team were blinded. Remote-monitored physiological data from implanted devices was used to provide matched control data in a time-stratified bidirectional case–crossover study providing a study approach that is statistically powerful and efficient in terms of the burden placed on patients. Access to hospital services for scheduled visits was limited due to public health measures put in place to limit the effect of COVID-19 meaning that follow up intervals differed between patients and not all patients with TE/CWE events underwent cardiac MRI.

In summary, our data show that a physiological risk score comprising measures of haemodynamic and physical activity when applied at baseline, accurately stratified patients with PAH for mortality at one, three and five years. When applied to data provided daily by implanted, regulatory-approved devices the novel risk score accurately identified change in risk following clinically indicated TE and clinical worsening. Thus, the remote physiological risk score may be of use in both clinical practice and as a research tool in clinical trials.

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Table 1: ASPIRE Cohort Demographics. Baseline demographics for 5820 patients with a diagnosis of pulmonary hypertension from the Sheffield ASPIRE Registry (REC 6/YH/0352).

	All PH groups n = 5820		Group I PAH n = 1771		Group II PH- LHD n = 1064		Group III PH- Lung n = 766		Group IV CTEPH n = 791		Group V PH- Miscellaneous n = 129	
Demographics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male sex (%)	39	-	31	-	34	-	54	-	50	-	40	-
Age at diagnosis (years)	63.0	15.8	58.5	15.9	72.1	9.5	67.2	11.0	62.7	14.9	59.6	12.9
WHO FC (I- IV)	3.01	0.64	3.00	0.63	2.85	0.60	3.21	0.64	2.90	0.61	3.07	0.68
BMI (kg/m^2)	29.2	7.2	27.9	6.6	30.9	6.9	28.9	8.1	29.8	7.2	27.6	8.0
Heart rate (bpm)	82	17	83	17	74	16	85	17	84	16	90	20
SpO2 (%)	94	4	94	4	95	4	94	4	93	4	93	6
Baseline ISWD (metres)	157	149	169	152	138	126	106	106	202	183	142	148
eGFR (mg/mmol)	64.7	5.6	68	19.3	56.2	21.1	68.2	20.0	67.0	17.7	66.7	24.1
EmPHasis 10 (max 50)	29	14	30	13	27	13	32	13	28	13	32	12
FEV1 (% predicted)	73	23	78	21	72	21	58	23	81	20	62	22
FVC (% predicted)	86	25	90	24	84	22	78	27	96	21	77	23
FEV1 /FVC Ratio (%)	69	13	72	11	69	10	61	17	68	10	66	15
TLCO (% predicted)	45.9	21.6	44.2	22.8	52.2	19.2	31.1	17.3	59.5	18.3	36.5	18.1
Mean RAP (mmHg)	11.1	6.2	10.3	6.0	14.9	5.9	10.0	5.6	10.7	5.6	10.6	5.8
Systolic PAP (mmHg)	72.5	20.6	75.3	21.3	65.5	18.4	66.7	11.0	77.6	20.0	70.1	18.7
Diastolic PAP (mmHg)	26.9	9.4	28.5	10.4	24.5	7.5	26.3	8.8	26.4	8.6	27.9	9.5
Mean PAP (mmHg)	44.5	12.1	46.6	13.1	40.9	10.4	41.8	10.8	45.5	11.3	44.8	11.1
PCWP (mmHg)	14	6	11	4	22	6	12	5	12	4	12	4
PVR (dynes)	603	402	725	444	337	244	535	337	648	373	619	392
TPR (dynes)	850	446	930	501	710	343	746	388	880	416	829	445
CO (L/min)	4.9	1.9	4.7	1.8	5.2	1.8	5.3	2.2	4.7	1.6	5.3	2.5
Cardiac Index ($L/min/m^2$)	2.6	0.9	2.6	0.9	2.8	0.8	2.8	1.1	2.4	0.7	2.9	1.2
Nitric Oxide Responder (%)	7	-	7	-	-	-	-	-	-	-	-	-

PH: Pulmonary Hypertension; PAH: Pulmonary Arterial Hypertension; PH: pulmonary hypertension; LHD: Left Heart Disease; CTEPH: Chronic Thromboembolic PH; WHO FC: World Health Organisation Functional Class; BMI: Body Mass Index; bpm: beats per minute; SpO2: Oxygen saturations; ISWD: Incremental Shuttle Walk Distance; eGFR: estimated Glomerular Filtration Rate; FEV1: Forced Expiratory Volume in 1 second; FVC: Functional Vital Capacity; TLCO: Transfer Factor; RAP: Right Atrial Pressure; PAP: Pulmonary Artery Pressure; PCWP: Pulmonary Capillary Wedge Pressure; SVO2: Venous oxygen saturations; PVR: Pulmonary Vascular Resistance; TPR: Transpulmonary Resistance; NO: Nitric Oxide.

Table *2:* Univariate and multivariate Cox Regression Model for clinical and haemodynamic parameters in patients with PH in the ASPIRE registry (REC 6/YH/0352).

	Univariate				Multivariate			
	Significance (p value)	Hazard Ratio	95% CI for HR Lower	Upper	Significance (p value)	Hazard Ratio	95% CI for HR Lower	Upper
Age at diagnosis (per 1 year)	<0.001	1.034	1.031	1.037	<0.001	1.030	1.025	1.035
Male sex	<0.001	1.282	1.192	1.381	<0.001	1.753	1.563	1.966
WHO Group I-V	<0.001	0.954	0.928	0.981	<0.001	0.889	0.854	0.926
WHO FC I-IV	<0.001	2.113	1.964	2.250	<0.001	1.348	1.203	1.512
ISWD (metres)	<0.001	0.996	0.995	0.996	<0.001	0.997	0.997	0.998
Mean RAP (per 1 mmHg)	<0.001	1.026	1.019	1.033				
Mean PAP (per 1 mmHg)	<0.001	1.006	1.003	1.009				
PCWP (per 1 mmHg)	0.454	0.997	0.991	1.004				
PVR (per 1 WU)	<0.001	1.036	1.028	1.044	<0.001	1.020	1.009	1.032
TPR (per 1 WU)	<0.001	1.035	1.027	1.042	0.001	1.016	1.006	1.025
SpO2 (per 1%)	<0.001	0.982	0.972	0.991				
SVO2 (per 1%)	<0.001	0.973	0.968	0.977				
CO (per 1L/min)	<0.001	0.875	0.853	0.897				
CI (per 1 L-min^{-1})	<0.001	0.819	0.779	0.862				
HRR (per 1 bpm)	<0.001	0.985	0.982	0.987	0.000	1.007	1.004	1.011
EmPHasis -10	<0.001	1.024	1.018	1.031				

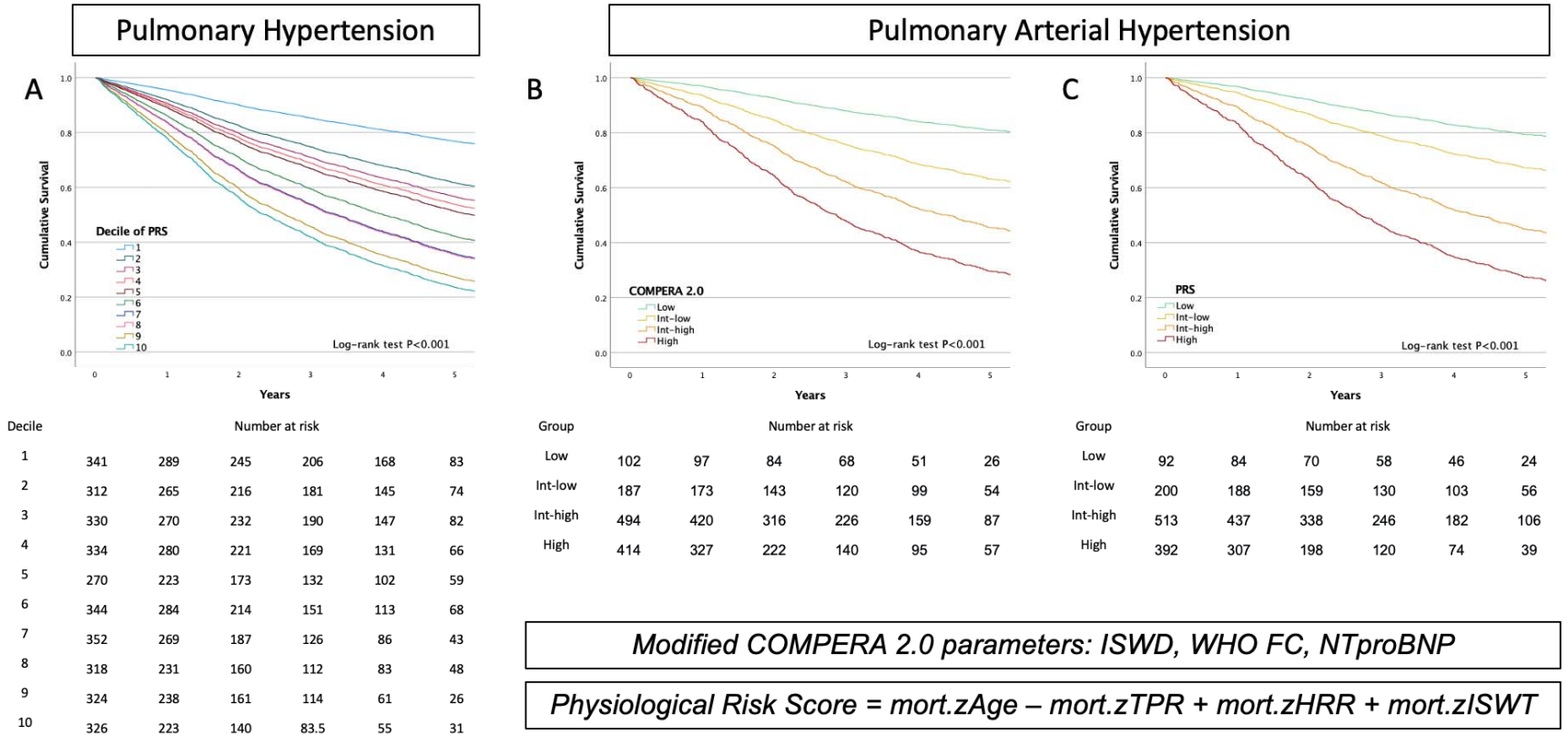


Figure 1: Risk stratification of patients with pulmonary hypertension and pulmonary arterial hypertension. A. Kaplan-Meier analysis of mortality stratified by baseline remote physiological risk score in patients with pulmonary hypertension from the ASPIRE registry. Individual physiological risk scores were calculated by summation of the mortality weighted z-score for age, resting heart rate, total pulmonary resistance and incremental shuttle walk test and patients separated into deciles of baseline risk (p<0.001 for each decile of risk). B. Kaplan-Meier analysis of mortality stratified by baseline COMPERA 2.0 scores. Kaplan-Meier estimated survival rates 1, 3 and 5 years after diagnosis for the low-risk group were 98%, 90% and 80%, respectively; for the intermediate-low risk group, 95%, 79% and 63%, respectively; for the intermediate-high risk group, 89%, 63% and 44%, respectively; and for the high-risk group, 83%, 45% and 32%, respectively (p<0.001 for between group comparisons). C. Kaplan-Meier analysis of mortality stratified by baseline 4-strata remote risk score. Kaplan-Meier estimated survival rates 1, 3 and 5 years after diagnosis for the low-risk group were 96%, 87% and 80%, respectively; for the intermediate-low risk group, 93.0%, 81% and 65%, respectively; for the intermediate-high risk group, 89%, 62% and 46%, respectively; and for the high-risk group, 83%, 45% and 28%, respectively (p<0.001 for between group comparisons). Physiological risk score = mort.zAge + mort.z.TPR + mort.zHRR - mort.zISWD.

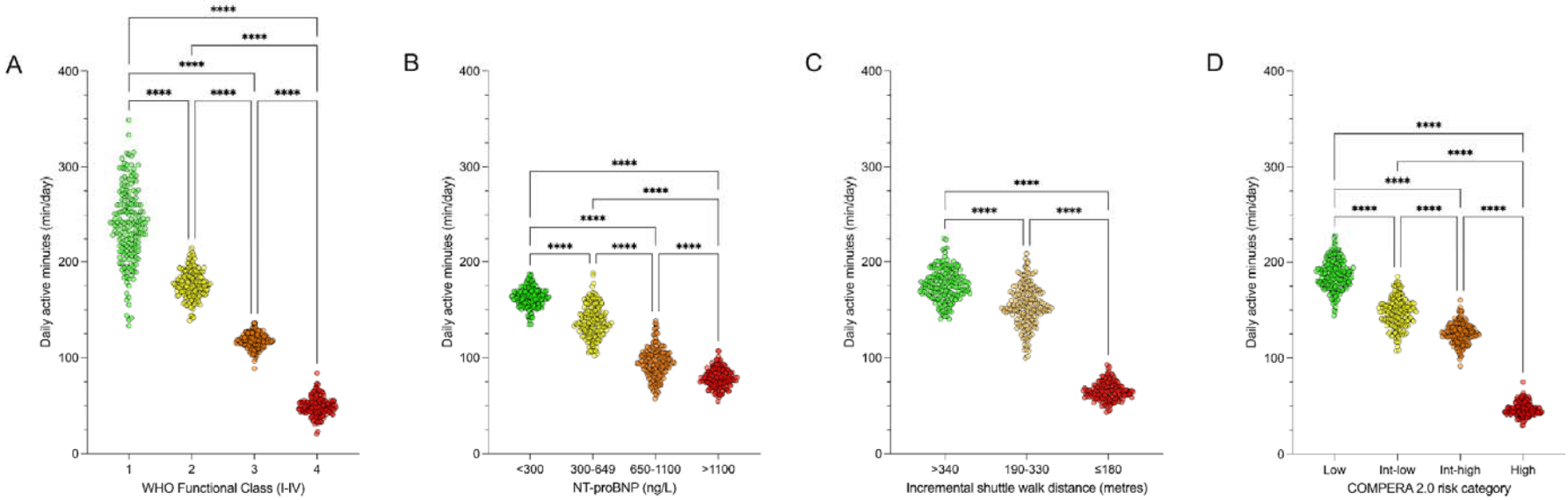


Figure 2: Mean daily physical activity of patients with pulmonary arterial hypertension in the first 6 months following ICM implantation stratified by established indicators of clinical risk. A: WHO Functional Class, B. NT-proBNP, C. Incremental shuttle walk and D. COMPERA 2.0 (one-way ANOVA with Dunnett's post-test correction ****p<0.0001).

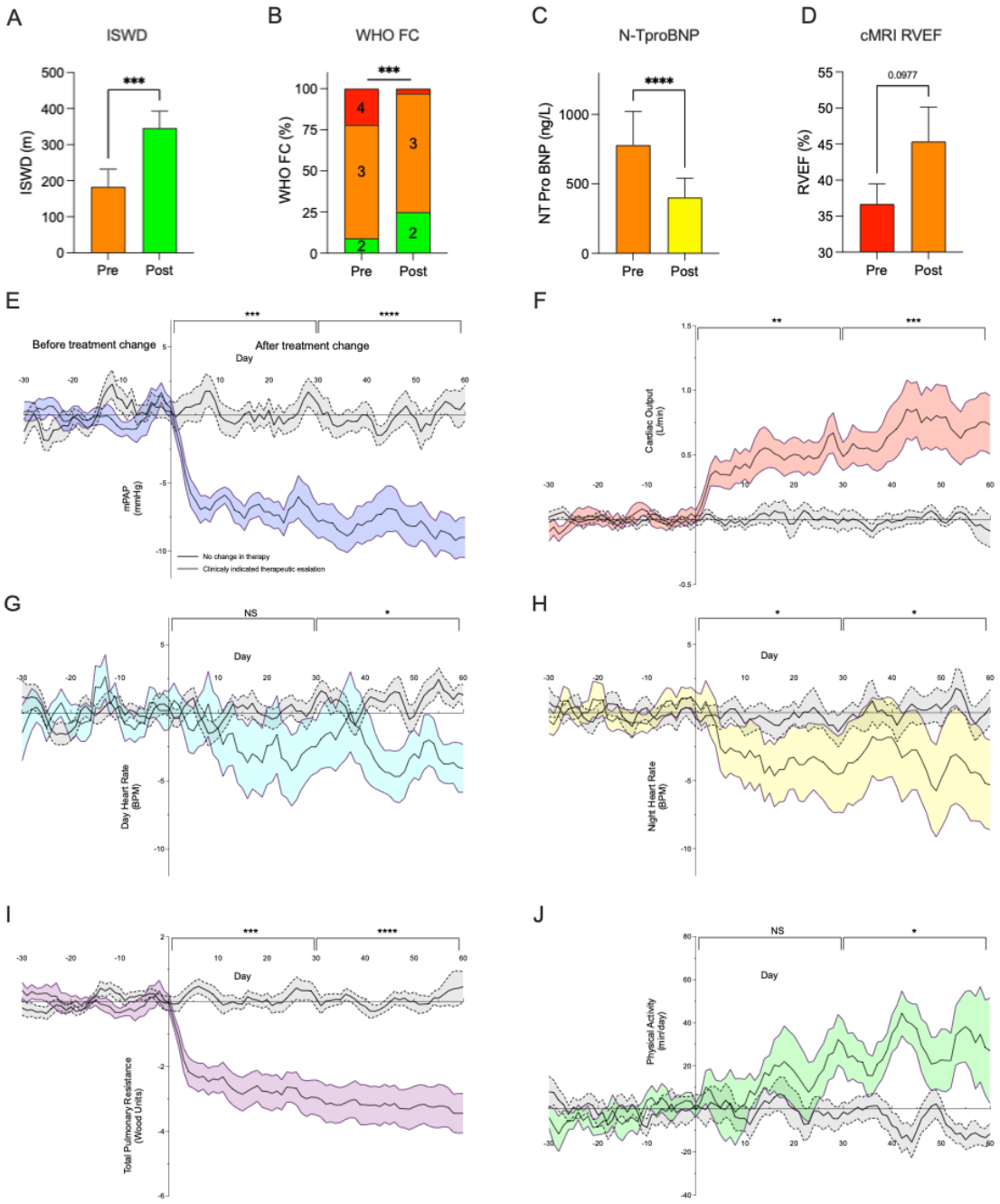


Figure 3: Remote monitored physiology following clinically indicated treatment change in patients with PAH and insertable cardiac and pulmonary artery pressure monitors.

Changes in A. Incremental shuttle walk distance (ISWD), B. WHO functional class (WHO FC), C. NT ProBNP (C, Wilcoxon, *p<0.05, n=18) and D. right ventricular ejection fraction from cardiac MRI (cMRI- RVEF, p=NS, n=9) pre and post clinically indicated therapeutic escalation (risk group: low-risk – green; int-low – yellow; int-high – orange; high – red). Following clinically indicated increase in therapy improvements in field walk test, WHO functional class and NT-proBNP were observed (p<0.05) with mean time to follow up of 5.1 months. Change from baseline in E. pulmonary artery pressure, F. cardiac output, G. day heart rate, H. night heart rate, I. total pulmonary resistance and J. physical activity following clinically indicated therapeutic escalation. Data is

presented with treatment change at day 0 with days –30 to day -1 as days preceding (left of the Y-axis), and days +1 to day +60 as days following treatment change (right of the Y-axis). Control group comprises 90-day periods from patients on stable therapy (grey). Treatment change n=18, mean +/-SEM; Remote monitored mean pulmonary artery pressure and total pulmonary resistance were reduced and cardiac output and physical activity increased compared to baseline at day 7, 4, 22 and 42 respectively (*p<0.05, p<0.01, ***p<0.001, ****p<0.0001 one-way ANOVA with Dunnett's correction).

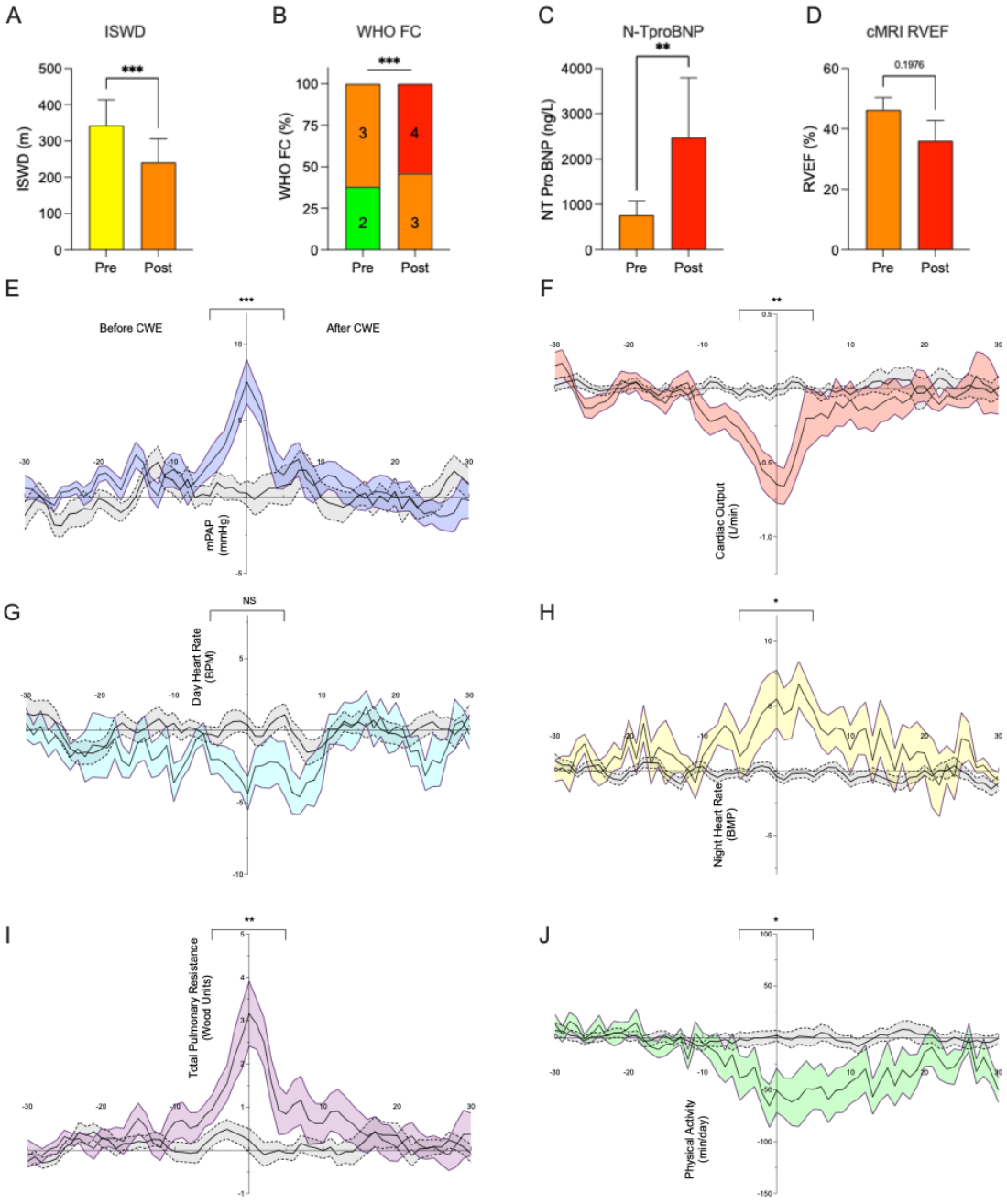


Figure 4: Remote monitored physiology following clinical worsening event in patients with PAH and insertable cardiac and pulmonary artery pressure monitors.

Changes in A. Incremental shuttle walk distance (ISWD), B. WHO functional class (WHO FC), C. NT ProBNP (A-C, Wilcoxon, *p<0.05, n=13) and D. right ventricular ejection fraction from cardiac MRI (cMRI- RVEF, p=NS, n=5) post clinical worsening event (CWE, risk group: low-risk – green; int-low – yellow; int-high – orange; high – red). CWEs led to deterioration in incremental shuttle walk test distance, WHO functional class and NT-proBNP (p<0.05). Change from baseline in E. pulmonary artery pressure, F. cardiac output, G. day heart rate, H. night heart rate, I. total pulmonary resistance and J. physical activity preceding a CWE. Data is presented with CWE at

day 0 with days –30 to day -1 as days preceding (left of the Y-axis), and days +1 to day +30 as days following CWE (right of the Y-axis). Control group comprises 60-day periods from patients with no CWE (grey). CWE n=13, mean +/-SEM; Remote monitored mean pulmonary artery pressure and total pulmonary resistance were increased and cardiac output and physical activity reduced 10 days prior to a clinical worsening event (*p<0.05, **p<0.01, ***p<0.001 paired Student's t-test).

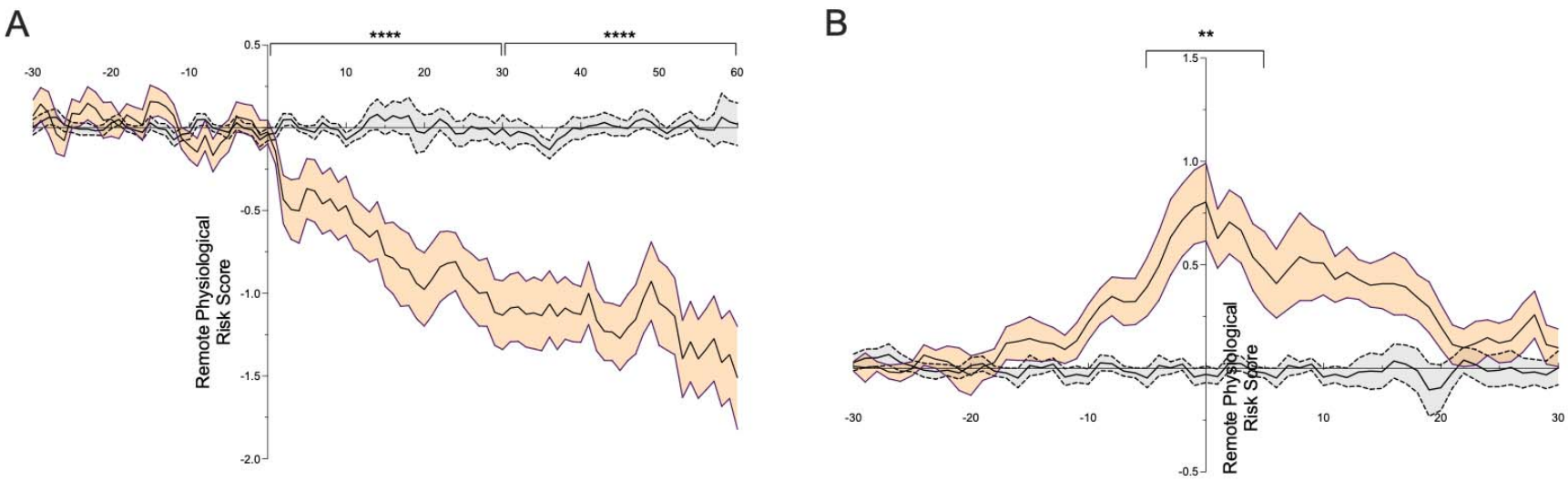
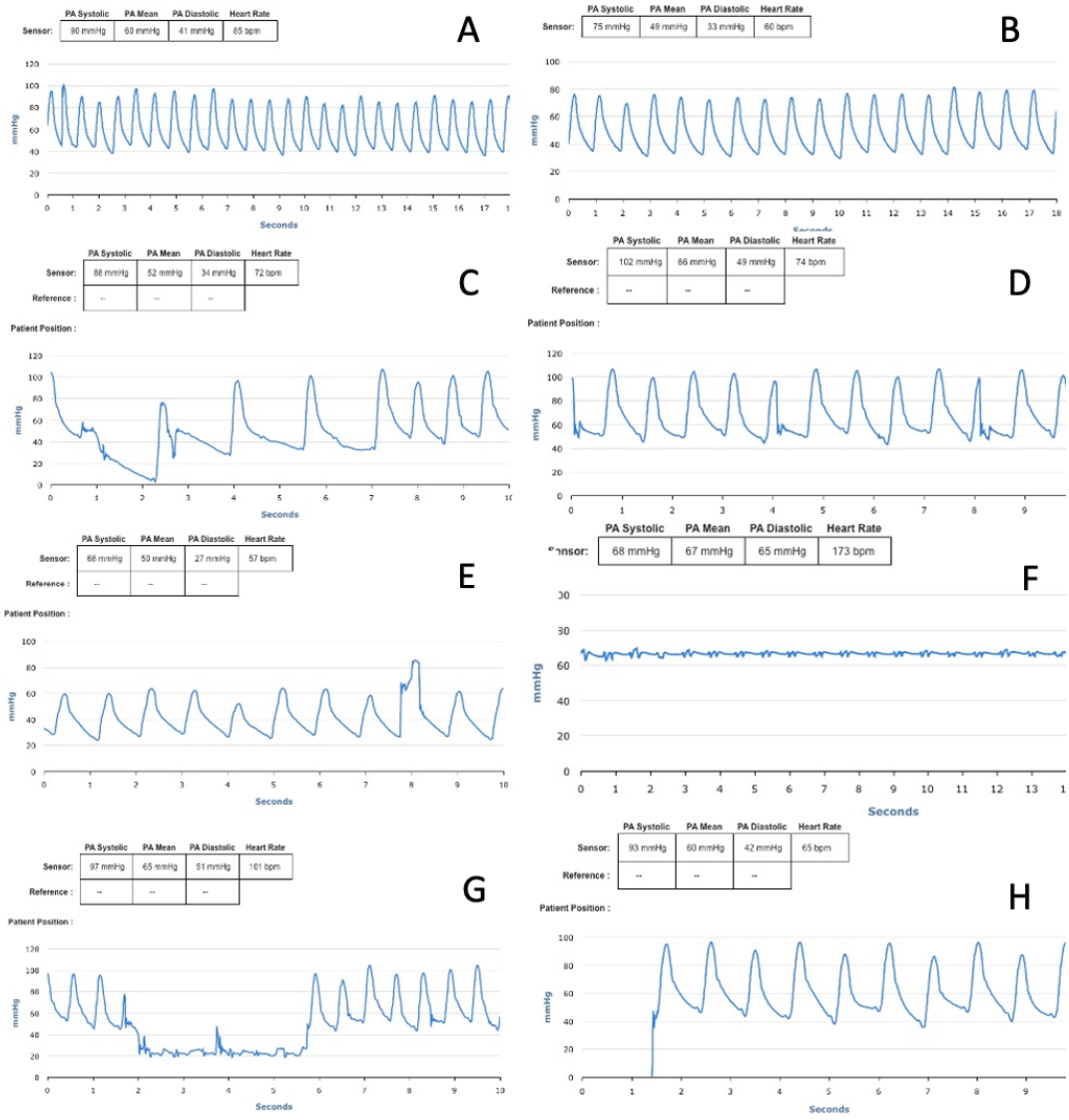


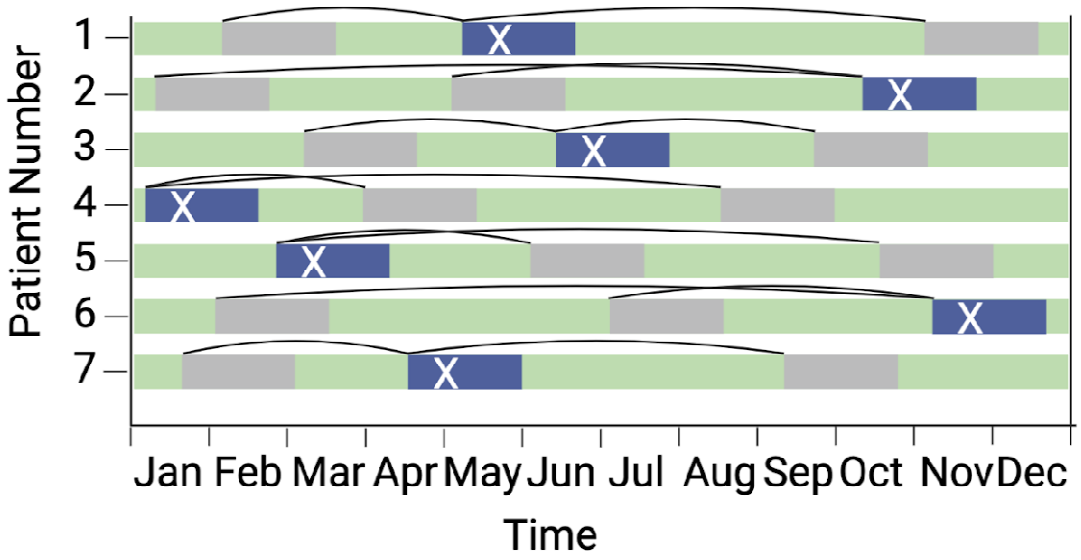
Figure 5: Effects of clinically indicated therapeutic escalation and clinical worsening events on remote pulmonary arterial hypertension risk score

Individual risk scores were calculated by summation of the mortality weighted z-score for age, resting heart rate, total pulmonary resistance and physical activity. Data is presented with A. therapeutic escalation (TE) or B. clinical worsening event (CWE) at day 0 with days –30 to day -1 as days preceding (left of the Y-axis), and days +1 to day +30 as days following TE/ CWE (right of the Y-axis). Control group comprises 60-day periods from patients with no TE or CWE (grey). TE n=18, CWE n=13, mean +/-SEM, one-way ANOVA with Dunnett's correction and paired Student's t-test, *p<0.05, ****p<0.0001).

Supplemental data



Supplemental Figure 1: Examples of non-clinically significant 'suspect' pulmonary artery pressure waveforms measured from a CardioMEMS device resulting from: A: Non-rested physiological state; B: rested physiological state; C: A pause followed by a compensatory bradycardia; D: Frequent ventricular ectopy; E: Non physiological waveform; F: Incorrect waveform frequency detected; G: Waveform damping; H: Non transmission of waveforms.



Supplemental Figure 2: Representative sampling of remote monitoring data for event and control periods in time-stratified bidirectional case–crossover study. Period of remote monitoring is indicated by green. Timepoints of clinician-directed therapeutic escalation or clinical worsening events are indicated by white X with the time 30-days preceding and 30-days (CWE) or 60-days (TE) following the event indicated in blue. Control time periods are indicated in grey.

Supplemental Table 1: Baseline demographics for patients with an implantable cardiac monitor

	n (%) or mean ± SD		
	Sheffield (n=50)	Cambridge (n=30)	Combined (n=80)
Age (years)	50 ± 15	57 ± 15	52.5 ± 14.9
Male sex (%)	12 (24)	7 (23.3)	19 (23.8)
BMI	30 ± 5	29 ± 7	30 ± 6
Race (% of group) Caucasian Asian Black	 44 (88) 2 (4) 4 (8)	 30 (100) 0 0	 74 (92.5) 2 (2.5) 4 (5)
Idiopathic PAH (n, %)	50 (100)	30 (100)	80 (100)
Mutation positive (n, %) BMPR2 ALK1 TBX4	 6 (12) 3 (6) 2 (4)	 2 (6.7) 1 (3.3) 0	 6 (7.5) 3 (3.8) 2 (2.5)
Years since diagnosis	8.5 +/- 4.8	8.6 +/- 5.8	9.0 +/- 5.22
Baseline resting heart rate (bpm)	75 ± 11	73.4 ± 13.3	74.6 ± 11.8
Night heart rate (bpm)	71.9 ± 10.9	72.9 ± 12.2	72.2 ± 11.2
Day heart rate (bpm)	81.0 ± 9.4	80.8 ± 10.9	80.9 ± 9.9
Heart rate variability (bpm)	95.5 ± 32.77	92.1 ± 36.6	95.5 ± 32.8
Physical activity (metres)	138.5 ± 93.6	150.5 ± 74.6	53.2 ± 14.9

Heart rate reserve (bpm)	9.1 ± 5.1	8.8 ± 4.8	9.0 ± 5.0
Baseline systolic BP (mmHg)	126.1 ± 18.0	127.5 ± 20.1	126.7 ± 18.7
Resting SpO_2 (%)	79.7 ± 11.5	97.7 ± 2.7	96.2 ± 2.9
WHO Functional class I II III IV	 1 (2) 20 (40) 24 (48) 5 (10)	 1 (3.3) 12 (40.0) 16 (53.3) 1 (3.3)	 2 (2.5) 32 (40) 40 (50) 6 (7.5)
ISWD (metres)	348 ± 247	N/A	
6MWD (metres)	N/A	402.7 ± 155.8	
NT-pro BNP (g/dl)	1158.3 ± 2711.0	543.1 ± 829.3	921.7 ± 2205.0
Nitric Oxide Responder positive	14 (28)	2 (6.7)	16 (20)
Right Heart Catheter Mean RA (mmHg) Systolic PAP (mmHg) Diastolic PAP (mmHg) PCWP (mmHg) Mean PAP (mmHg) CO (L/min) PVR (Dynes.sec.cm) CI (L/min/m^2) SVO_2 (%) TPR (Dynes.sec.cm)	 10.7 ± 7.2 84.8 ± 30.2 35.2 ± 13.5 10.4 ± 4.1 52.8 ± 16.3 4.2 ± 1.7 974.8 ± 618.5 2.4 ± 1.0 60.9 ± 20.8 1212 ± 687	 7.3 ± 2.1 71.9 ± 20.9 27.8 ± 8.1 9.7 ± 2.7 43.9 ± 13.4 4.3 ± 1.4 772.2 ± 537.9 2.3 ± 0.8 69.7 ± 7.5 928 ± 544	 9.4 ± 6.1 79.8 ± 27.4 32.4 ± 12.2 10.2 ± 3.6 49.5 ± 15.8 4.3 ± 1.6 898.9 ± 594.3 2.4 ± 0.8 64.3 ± 17.4 1105 ± 648
Pulmonary Function test FEV1/ FVC ratio	 0.80 ± 0.10	 0.70 ± 0.11	 0.70 ± 0.10

Supplemental table 2: ICM implant details

	Sheffield n (%)	Cambridge n (%)
Primary operator Physician Highly specialised cardiac physiologist	 50 (100) 0	 30 (100) 0
Device implanted In catheter lab In a clinic setting	 4 (8) 46 (92)	 3 (10) 27 (90)
Device complications <30 days	1 (1.8)	2 (6.7)
Device complications >30 days	0	0

Supplemental table 3: ICM Adverse events

	Number of occurrences	Action taken
Serious Adverse events	0	NA
Bleeding	0	NA
Infection	0	NA
Device erosion	1	Explanted, allowed to heal and new device implanted

Supplemental Table 4: Baseline demographics: FIT-PH

Baseline Demographics (n=28)	n (%) or mean ± SD
Sex (female)	21 (75)
Age (years)	48.9 ± 18.1
Ethnicity Caucasian Asian	 25 (89) 3 (11)
Diagnosis – Group 1 (PAH) Idiopathic / Heritable PAH Connective tissue disease Congenital heart disease	 25 (89) 2 (7) 1 (4)
PH-specific gene mutation identified BMPR2 ALK1 Other	4 (14) 2 (7) 1 (4) 1 (4)
Acute vasoreactivity to nitrous oxide	10 (36)
Years since diagnosis	7.2 ± 4.6
WHO FC I II III IV	 0 0 22 (79) 6 (21)
BMI (kg/m^2)	28 ± 6
EmPHasis 10 score (max 50)	29 ± 13
Systolic BP (mmHg)	122 ± 17
Resting heart rate (beats per minute)	76 ± 11
Resting SpO2 (%)	95 ± 4
12-Lead ECG (normal sinus rhythm)	26 (93)
NT Pro BNP (pg / ml)	1410 ± 3537
ISWD (metres)	324 ± 251
FEV1 (L)	2.6 ± 0.8
FVC (L)	3.6 ±1.1
FEV1/FVC ratio (%)	75 ± 7
TLCO (mmol/min/kPa) (%)	5.4 ± 2.2
Right Heart Catheter Mean RAP (mmHg) Systolic PAP (mmHg) Diastolic PAP (mmHg) Mean PAP (mmHg) PCWP (mmHg) SV02 (%) Cardiac Output (L/min) PVR (Dynes.sec.cm) Cardiac Index ($L/min/m^2$) TPR (Dynes.sec.cm)	 9.4 ± 4.8 78.6 ± 25 33..1 ± 11.2 50.8 ± 11.2 10.4 ± 4.5 63 ± 20.7 4.6 ± 1.6 812 ± 488 2.5 ± 0.7 1032 ± 560
Mortality events	3 (11)

Supplemental Table 5: Baseline therapy – FIT-PH

Baseline Therapy (n=28)	N (%) or mean ± SD
CCB (PAH indication)	13 (46)
PDE-5 inhibitor	27 (96)
ERA	23 (82)
Selexipag	4 (14)
Riociguat	1 (4)
Nebulisers	3 (11)
Intravenous prostanoid	6 (26)
Single oral Dual oral Triple oral therapy Oral + nebulisers Oral + intravenous Intravenous only	0 8 (29) 9 (32) 3 (11) 6 (26) 0
Loop diuretic	16 (57)
MRA	7 (25)
Oral anticoagulant DOAC Warfarin	 0 2 (7)
Concomitant medication	26 (93)

CCB: Calcium Channel Blocker; PAH: Pulmonary Arterial Hypertension; PDE5: Phosphodiesterase-5; ERA: Endothelin Receptor Antagonist; MRA: Mineralocorticoid Receptor Antagonist; DOAC: Direct Oral Anticoagulant.

Supplemental Table 6: Total remote monitoring data collected during FIT-PH

	Mean ± SD
Weeks since PAP monitor implant Cumulative patient data from PAP monitors (weeks)	119.0 ± 48.7 3333
Weeks since LinQ implant Total patient data from LinQ (weeks)	127.9 ± 30.8 10,321

Census date 01.03.2023

Supplemental Table 7: Serious adverse events and adverse events reported in the FIT-PH study.

Adverse Events	Number of occurrences	Action taken / further information
Serious Adverse Events	0	NA
Bleeding	1	Minor haemoptysis, resolved with no intervention
Infection	0	NA
Vascular injury	0	NA
Pulmonary Embolism	0	NA
Drug interaction	1	Selexipag and clopidogrel. Clopidogrel replace with prasugrel.