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Establishing minimally important differences for cardiac MRI endpoints in pulmonary arterial hypertension

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Abstract

Introduction: Cardiac MRI (CMR) is the gold standard technique to assess bi-ventricular volumes and function and is increasingly being considered as an endpoint in clinical studies. Currently, with the exception of right ventricle (RV) stroke volume and RV end-diastolic volume, there is only limited data on minimally important differences (MIDs) reported for CMR metrics. Our study aimed to identify MIDs for CMR metrics based on FDA recommendations for a clinical outcome measure that should reflect how a patient feels, functions or survives.

Methods: Consecutive treatment-naïve patients with PAH between 2010 and 2022 who had two CMR scans (at baseline prior to treatment and 12 months following treatment) were identified from the ASPIRE registry. All patients were followed up for one additional year after the second scan. For both scans, cardiac measurements were obtained from a validated fully automated segmentation tool. The MID in CMR metrics was determined using two distribution-based (0.5 standard deviation and minimal detectable change) and two anchor-based methods (change difference and generalised linear model regression) benchmarked to how a patient "feels" (emPHasis-10 questionnaire), "functions" (incremental shuttle walking test) or "survives" for one-year mortality to changes in CMR measurements.

Results: 254 patients with PAH were included (aged 53±16 years, 79% female, and 66% categorised as intermediate risk based on 2022 ESC/ERS risk score,). We identified a 5% absolute increase in RV ejection fraction and a 17ml decrease in RV end-diastolic or end-systolic volumes as the MIDs for improvement. Conversely, a 5% decrease in RV ejection fraction and a 10ml increase in RV volumes were associated with worsening.

Conclusion: This study establishes clinically relevant CMR MIDs for how a patient feels, functions or survives in response to PAH treatment. These findings provide further support for the use of CMR as a clinically relevant clinical outcome measure and will aid trial-size calculations for studies using CMR.

Introduction

In patients with pulmonary arterial hypertension (PAH) symptoms and survival are determined primarily by right ventricular function. In PAH, a progressive pulmonary vasculopathy results in elevation of mean pulmonary arterial pressure (mPAP) and an increase in right ventricle (RV) afterload [1]. With disease progression and chronically elevated mPAP, the RV undergoes remodelling, resulting in either adaptation and maintenance of output [2] or maladaptation, RV failure and consequently reduced survival [3]. Cardiac MRI (CMR) is the gold standard for assessing the RV and shows potential in the assessment of PAH [4]. Impairments of RV function and associated increases in RV volumes can be detected and quantified by CMR, enabling prediction of clinical worsening and mortality [5] and aids risk stratification [6]. In addition, CMR is sensitive to improvements in RV function following PAH therapy [7–10] and detects a larger treatment effect than the 6-minute walk [11]. In this context, CMR is an important tool for risk stratification and monitoring of disease and treatment response in PAH [4].

Phase four clinical studies of PAH therapies have recently utilised CMR as a primary endpoint in addition to other composite outcomes [9, 10]. Assessing treatment response with CMR necessitates clinically relevant thresholds in order to determine improvement or worsening. However, only RV stroke volume measured on pulmonary artery phase-contrast flow imaging has established thresholds [12], while those for volumetric CMR measurements on cine imaging with the exception of right ventricular end-diastolic volume remain unvalidated [13]. The introduction of automatic volumetric CMR measurements assessing RV changes over time has several advantages. It offers excellent repeatability in scan-rescan assessment and has higher accuracy than manual assessment [14]. In addition, results are generalisable across different centres and MRI systems, allowing standardised comparisons independent of the location of scan [14–16].

The Federal Drug Administration (FDA) has highlighted the need to identify clinical outcome measures for PAH therapy trials that reflect how a patient “feels, functions and survives” [17]. To reflect this, we have

aimed to identify clinically relevant thresholds for change in automatically derived CMR RV and LV measurements, benchmarking against patient-reported outcome measures ("feels"), exercise testing ("functions") and mortality ("survives"). Our results should aid the management of patients in the clinic by identifying clinically meaningful changes in key CMR metrics and aid researchers by informing power calculations and the selection of endpoints for clinical studies using CMR.

Methods

Study sample

Adult patients with PAH were identified from the "Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre" (ASPIRE) registry [18] between January 2010 and January 2022. Diagnosis of PAH was based on mPAP >=25mmHg and PAWP <=15mmHg and PVR>= 3 Wood Units, measured by right heart catheterisation (RHC). Patients were eligible for inclusion if they had: 1) baseline CMR prior to starting treatment and within 48 hours of PAH diagnosis, 2) follow-up CMR at 12-24 months and 3) at least one-year follow-up after the follow-up scan. Patients were excluded if they did not have complete short-axis stack imaging for both baseline and repeat scans. The local ethics committee and institutional review board approved this study (ASPIRE, ref: c06/Q2308/8).

Imaging procedures

MRI protocol

CMR was performed with 1.5 Tesla MRI systems from GE (Signa HDx, General Electrics Healthcare). Short-axis cine images were acquired using a cardiac-gated multislice balanced steady-state free precession sequence (20 frames per cardiac cycle, section thickness 10mm, 0mm inter-section gap, field of view 480mm, acquisition matrix 256 × 200, flip angle 60°, BW 125 KHz/pixel, TR/TE 3.7/1.6ms). A stack of images in

the short-axis plane was acquired, fully covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave triggered acquisition or largest volume. Patients were supine with a surface coil and with retrospective ECG gating.

Image analysis

An in-house deep-learning cardiac MRI segmentation tool was used to obtain fully automatic measurements [14]. The segmentation tool was trained in a multi-centre, multi-vendor and multi-pathology dataset and was previously validated by assessing: (i) Accuracy against same-day invasive pulmonary hemodynamics and phase contrast flow imaging. (ii) Repeatability in a same-day scan-rescan cohort. (iii) Generalisability in an external testing cohort. (iv) Mortality prediction in a large cohort with multiple cardiac and lung pathologies. The automatic contours included trabeculations in the blood pool and were obtained using MASS software (MASS, research version 2020; Leiden University Medical Center).

Clinical parameters

The emPHasis-10 questionnaire (E-10) is a patient-reported outcome measure to assess health-related quality of life in patients with PAH was completed at baseline and at the time of the follow-up scan from 2014 onwards. Each patient completed ten questions ranked on a scale of 0 to 5, with a lower score indicating a better quality of life [19]. The incremental shuttle walking test (ISWT) was performed as part of routine patient evaluation according to the standard method [20]. Patients complete a 10m length keeping in time to an external audible signal. Level one consists of three lengths (30m) and each additional level adds one extra 10m length to the preceding level. Each level takes 1 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 the required pace. The REVEAL 2.0 and the 2022 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) risk scores were calculated from composite clinical parameters [21, 22] and

modified to include the incremental shuttle walk test instead of the 6-minute walking test [6, 23]. Mortality data were collected from the electronic records of the National Health Service (NHS) Personal Demographics Service. The NHS automatically updates the mortality records once a death is registered in the United Kingdom. All patients were followed up as part of the national service specification for patients with pulmonary hypertension for a minimum of 12 months.

Statistical analysis

Baseline characteristics are presented as proportions, means ± standard deviation (SD), or medians and interquartile ranges (IQR). For each CMR parameter, both the absolute and relative differences were calculated. The absolute difference was determined by subtracting the baseline measurement from the follow-up measurement, while the relative difference was calculated as the ratio of the absolute difference to the baseline measurement.

We employed four methods to derive the minimal important difference (MID) estimates; two distribution-based and two anchor-based methods (Table 1). Initially, Pearson's correlation analysis was used to determine at least a weak correlation ($r > 0.20$) between the change CMR measurements and the anchor [24, 25]. The difference in CMR parameters and difference in E-10 or ISWT were regressed onto a scale of 6 units using the Z-score normalisation to assess the correlation of these changes. Any CMR measurement failing to meet the correlation threshold was subsequently excluded from further MID analysis [24].

Anchors for how a patient “feels” were determined using a patient-reported outcome measure (E-10) and “functions” using an assessment of exercise capacity (ISWT). Patients were considered to have improved, remained stable or worsened between baseline and follow-up, based on a change of 6 points in E-10 [26, 27] or 47.5 m in ISWT [28, 29]. For how a patient “survives”, changes in CMR measurements in patients who survived one year post the follow-up scan were compared to patients who did not. For the anchor-based

method, we derived MID estimates using change difference and regression analysis. The change difference was identified as the difference between the mean change in CMR measurements in patients who had improved or worsened (defined by the anchor) and the mean change in stable patients. The change difference method effectively adjusts the degree of change in the improved or worsened group according to the change observed in the stable group. For the regression analysis, we employed a generalised linear regression model (GLM) to predict the difference in scores (DScore) between baseline and follow-up CMR measurements, as represented by the following formula: DScores = k + βb Xbetter + βw Xworse + βs Xstable. The DScore represents the change in CMR parameters, and patient status (defined by the anchor as better (Xbetter) or worse (Xworse)) was entered as dummy variables in the model. The coefficients of better (βb) and worse (βw) in the regression model estimated the incremental difference in scores when patient status transitioned to better or worse compared to stable patients.

In the distribution-based approach, the MID was estimated based on the distribution of CMR measurements within each patient group (improved/worsened). In the first distribution method, the MID was estimated as 0.5 standard deviations (SD) of the change in CMR measurements [30]. In the second distribution method, the minimal detectable change (MDC) was calculated using the formula: MDC = 1.96 × √2 × standard error of measurement (SEM). The SEM was calculated by multiplying the SD of the difference in cardiac MRI measurements by the square root of one minus its reliability coefficient. Previously published consistency intraclass correlation coefficient (ICC) values were used as the reliability coefficient of the CMR measurements [31]. Distribution-based methods were employed to facilitate the interpretation of the anchor-based method results. The SEM describes the variability between the observed and the true measurements. Changes in CMR measurements smaller than the corresponding SEM are more likely to represent an error of measurement rather than genuine changes [32]. In instances where the anchor-based MIDs were less than the SEM (i.e., indistinguishable from measurement error), the SEM was utilised as the

MID [24].

Statistical analyses were carried out using the lifelines and pingouin Python libraries [33, 34] with a significance threshold of 0.05. Graphs were produced using the Matplotlib library [35] and Prism 9 (GraphPad Software, La Jolla CA, USA).

Results

A total of 254 treatment-naïve patients with PAH were included (Figure 1). Patients were aged 53±16 years, with 79% female, 82% categorised as WHO functional class 3 and with an intermediate risk for mortality of 68% and 66% on REVEAL 2.0 and ESC/ERS 2022 risk models, respectively. 41% had PAH associated with connective tissue disease, 37% had idiopathic PAH and 22% had other types of PAH. The median mPAP was 50mmHg (IQR 41 to 59) and median pulmonary vascular resistance was 812 dyns.s.cm^{-5} (IQR 526 to 1154). The E-10 score was 31 ± 12 and ISWT walking distance was 207 m ± 175. Baseline patient characteristics are shown in Table 2.

The median duration between the baseline and repeat scan was 12 months (IQR 7 to 16 months). Between the two scans patients were treated with phosphodiesterase 5 inhibitors (86%), endothelin receptor antagonists (72%), parenteral prostanoid (17%) and other medications (4%), with 32 % receiving monotherapy, 48% dual combination and 20% triple combination therapy. During follow-up after the repeat scan, 25/254 (10%) patients had died at 12 months and 123/254 (48%) patients died during a median period of 5 years from baseline (IQR 3 to 7).

Table 3 shows the mean CMR measurements at baseline and follow-up for the different patient groups. The absolute differences in right ventricular ejection fraction (RVEF) between baseline and follow-up have been reported in nine studies [8, 10, 11, 36–41] with a total of 321 treatment-naïve patients and their pooled results

compared to the current study are shown in Supplemental Figure 1 and presented in detail in Supplemental Table 1. The pooled mean difference in RVEF at one year was 6%, 95% CI (3 to 8) compared to 7%, 95% CI (5 to 9) in our study.

Minimal important difference for how a patient "feels, functions or survives"

E-10 and ISWT were performed mostly on the same day as the CMR and within two weeks, with a median time between CMR and E-10 of 0 (IQR 0 to 0) days and between CMR and ISWT of 0 (IQR 0 to 8) days. Paired baseline and follow-up E-10 (n = 118) and ISWT (n = 146) categorised patients into improved (n = 42 (35%) for E-10 and n = 57 (39%) for ISWT), stable (n = 55 (47%) for E-10 and n = 64 (44%) for ISWT), and worsened (n = 21 (18%) for E-10 and n = 25 (17%) for ISWT) (Table 2). The correlation between CMR parameters and E-10 and ISWT was weak for RV parameters; RVEF (r = -0.25, r = 0.20), right ventricular end-diastolic volume (RVEDV) (r= 0.28, r = -0.28) and right ventricular end-systolic volume (RVESV) (r = 0.32, r = 0.34). None of the LV parameters or RV stroke volume (r = 0.10 for both E-10 and ISWT) showed a sufficient correlation with the anchors. The mean MID values for absolute and relative improvement and worsening using the different MID methods are shown in Figure 2 and Supplemental Figure 2. In summary, the overall MID means and range of means across methods for improvement were as follows: 5% (3% to 9%) for RVEF, -17ml (-6ml to -27ml) for RVEDV and -17ml (-11ml to -24ml) for RVESV. For worsening, the values were -5% (-3% to -9%) for RVEF, 11ml (3ml to 19ml) for RVEDV and 10ml (3ml to 17ml) for RVESV (Figure 3). The highest relative change, indexed to the baseline value, was observed for RVEF (22% for improvement and -19% for worsening) (Supplemental Figure 2).

Discussion

Identifying clinically relevant thresholds for changes in CMR metrics that reflect how a patient "feels, functions or survives" has important implications for patient monitoring and the selection of therapy trial

endpoints. To the best of our knowledge, this is the first study to compare changes in CMR metrics to health-related quality of life in PAH in addition to measures of function and mortality and the first to assess clinically relevant MIDs for automatic CMR measurements. MIDs for CMR metrics were identified using various distribution-based and anchor-based methods in an effort to generate reliable estimates [42]. The MIDs obtained using the change in E-10 score, ISWT walking distance and survival as anchors were remarkably consistent across methods and anchors, reinforcing the robustness of the MID estimates. Only RV metrics sufficiently correlated with the anchors to allow for MID calculations.

In this study of 254 patients, we observed a mean absolute difference of 7% in RVEF post-PAH treatment at an average of one-year follow-up. Our result was comparable to the pooled estimate (6% mean difference in RVEF) identified from nine PAH studies, including 321 PAH patients with pre- and post-treatment RVEF measurements at 9 to 12 months. Two studies assessed change at 4 months following bosentan therapy: Benza et al. showed an absolute increase of 3% in RVEF in 84 patients [9] and Wilkins et al. reported an increase in RVEDV of 6ml and a decrease of RVESV of 2ml in 12 patients [43]. Van de Veerdonk et al. assessed 52 patients at baseline and at 5-year follow-up and found that a 3% absolute reduction in RVEF was associated with a lower survival rate in patients with decreased pulmonary vascular resistance [38]. Our study identifies a 5% increase in RVEF and a 17ml decrease in RVEDV and RVESV as MIDs for improvement, while a 5% decrease in RVEF and a 10 ml increase in RV volumes were associated with worsening.

CMR has been shown to be sensitive to change in response to treatment with CMR detecting a larger treatment effect than the 6-minute walk test [11]. Bradlow et al. previously estimated post-treatment thresholds for RV changes based on four studies with a total of 57 PAH patients [7]. Although they suggested an absolute difference in RVEF of 3% and RV volumes of 10ml as thresholds, these observations were

minimally detectable changes based on the repeatability of the measurement and not benchmarked against clinically relevant outcomes such as changes in quality of life, exercise capacity or mortality. In contrast, in our study we have benchmarked CMR parameters against measures of how a patient "feels, functions or survives". Until now, the only CMR parameters with a clinically relevant and validated threshold in PAH are RV stroke volume derived from phase-contrast flow imaging [12] and RV end-diastolic volume measured from trans-axial cine images [13]; RV stroke volume was anchored to a six-minute walking test, with 10ml change identified as a threshold for important clinical effect, whereas RV end-diastolic volume was anchored to a change in WHO functional class with an 11% relative change identified as clinically relevant. In this study, we compared the change in CMR cine imaging to changes in patient-reported outcome measures (E-10 health-related quality of life) and exercise capacity (ISWT walking distance). E-10 elicits how the patient "feels" with domains reflecting the burden of breathlessness, fatigue and anxiety on patients with PAH [19], whilst the ISWT reflects how a patient "functions" by assessing exercise capacity [23, 29, 44]. Both E-10 and ISWT have established MIDs, can assist in risk stratification of patients and have prognostic value, making them ideal benchmarks for assessing how a patient feels and functions [23, 26]. However, it must be noted that the E-10, ISWT and CMR all measure different components, confirmed by the weak correlation between differences in RV measurements and changes in E-10 and ISWT and therefore worsening in quality of life and exercise capacity can occur despite improvements in RV function. Despite being able to demonstrate that CMR metrics can detect MIDs for how a patient "feels, functions or survives" a composite endpoint that includes each of these domains will be superior to using a metric that focuses on a single measure such as cardiac function. Nonetheless, this study does provide further evidence for using CMR as a primary trial endpoint in studies of PAH therapies by providing evidence that changes in key CMR metrics do reflect changes in how a patient feels and functions.

While an absolute change in CMR measurements gives an indication of direction, it does not take into account the baseline state of the patient to contextualise the magnitude of change. This may be relevant in

patients with more severe disease where relative change is likely to be more sensitive to disease progression by accounting for a patient's pre-treatment baseline and therefore should be considered alongside absolute changes in metrics [45]. In the current study, trabeculations were included in the blood pool. Further work to establish MIDs for CMR measurements excluding trabeculations would be of value and as technology evolves there is a need to develop standardised approaches to CMR measurements of the right ventricle.

Limitations

The major limitation of any longitudinal retrospective study is the inherent risk of selection bias. Inevitably, patients who survived until follow-up CMR imaging have had a less severe disease course compared to those who died. However, patients having follow-up imaging might have been selected because the treating physician felt they were more at risk of deterioration and required additional monitoring; in our institution, CMR imaging is regularly performed as part of routine follow-up in preference to echocardiography. Furthermore, our findings are based on a single-centre cohort and our mortality prediction thresholds are largely exploratory in nature and should be validated in external cohorts. Given the emergence of prospective studies using CMR imaging as a trial endpoint and the increasing use of patient-reported outcome measures, consideration should be made into pooling data from such studies to refine our exploratory thresholds for how a patient feels, functions or survives. Larger data sets would also allow for the analysis of potential differences based on disease type (IPAH versus PAH-CTD) and sex differences [46, 47]. E-10 was developed in 2014 and therefore patients included from 2010 - 2014 were only assessed with ISWT. Finally, we have used the ISWT rather than the 6MWT as a measure of exercise capacity. The ISWT has the benefit over the 6MWT in that it is a maximal test and does not have a ceiling effect [23, 48] and thresholds exist for minimally important differences [28, 29]; however, data are more limited compared to the 6MWT in patients with PAH. Further study of CMR MIDs benchmarked to other measures of exercise capacity including 6MWT distance is required taking into account established MIDs for 6MWT [47].

Conclusion

We have shown that CMR can identify MIDs for how a patient feels, functions or survives. In doing so this study provides further evidence that CMR has the characteristics of a clinical outcome measure. In addition, the findings of this study and the description of MIDs will aid trial-size calculations for studies using CMR.

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Tables

Table 1: Methods employed to calculate the minimal important difference (MID)

Method	Type	Definition
0.5 standard deviation (SD)	Distribution-based	Estimated as 0.5 times the SD of the change in CMR measurements within each patient group (improved/worsened).
Minimal Detectable Change (MDC)	Distribution-based	Calculated based on the standard error of measurement (SEM). The SEM was calculated by multiplying the SD of the change in CMR measurements by the square root of (1 - reliability coefficient). The formula applied was: MDC = $1.96 \times \sqrt{2} \times$ SEM.
Change Difference	Anchor-based	Difference between the mean change in CMR measurements in patients who had improved or worsened (according to the anchor) and the mean change in stable patients.
General Linear Regression (GLM)	Anchor-based	Determined by the estimated coefficients for improvement and worsening, derived from a regression analysis using the anchor as a predictor for changes in CMR measurements.

Table 2: Baseline characteristics

	PAH *N = 254*
***Age** (years)*	55 (42 to 66)
***Sex** (female)*	201 (79%)
***BSA** (m^2)*	1.80 ± 0.35
PAH subcategory	
IPAH	94 (37%)
CTD	105 (41%)
CHD	21 (8%)
Portal hypertension	16 (6%)
other PAH	18 (7%)
WHO functional class	
II	10 (4%)
III	210 (83%)
IV	34 (13%)
REVEAL 2.0 score	
≤ 6	11 (4%)
7 - 8	173 (68%)
≥ 9	70 (28%)
ESC/ERS 2022 risk	
Low	18 (7%)
Intermediate	169 (66%)
High	67 (26%)
RHC parameters	
mPAP (mmHg)	50 (41 to 59)
PVR (dyns.s.cm^{-5})	812 (526 to 1154)
PAWP (mmHg)	10 (8 to 12)
RA mean (mmHg)	9 (6 to 14)
CO (L/min)	4 (3 to 5)
SvO_2 (%)	64 (58 to 70)
Heart rate (bpm)	77 (69 to 89)
PAH medication	
Sildenafil	199 (78%)
Tadalafil	20 (8%)
Ambrisentan	87 (34%)
Bosentan	33 (13%)
Macitentan	62 (24%)
Parenteral prostanoid	43 (17%)
Other	11 (4%)
Therapeutic strategy	
Monotherapy	74 (32%)
Dual combination	111 (48%)
Triple combination	45 (20%)

PAH, pulmonary arterial hypertension; BSA, body surface area; CHD, congenital heart disease; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; WHO, World Health Organisation; RHC, right heart catheterization; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary arterial wedge pressure; SV, stroke volume; CO, cardiac output; SvO2, mixed venous oxygen saturation; PDE 5, phosphodiesterase 5 inhibitors; ERA, endothelin receptor antagonists. Data presented as mean ± standard deviation or median (interquartile range).

Table 3: Changes in CMR measurements and clinical parameters: benchmarked to changes in how a patient feels (EmPHasis-10, n = 118), functions (incremental shuttle walking test, n = 146) or survives (one-year mortality post follow-up, n = 254)

	Improved		**Stable**		**Worsened**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
E-10	(n=42)		(n=55)		(n=21)	
E-10 (points)	37 ± 10	21 ± 11	29 ± 12	29 ± 12	24 ± 10	37 ± 7
RVEF (%)	32 ± 12	42 ± 13	34 ± 12	42 ± 10	38 ± 10	43 ± 8
RVEDV (ml)	208 ± 66	182 ± 59	200 ± 78	201 ± 74	174 ± 69	163 ± 57
RVESV (ml)	146 ± 60	110 ± 53	138 ± 68	122 ± 60	112 ± 56	94 ± 40
ISWT	(n=57)		(n=64)		(n=25)	
Walking distance (m)	249 ± 181	409 ± 197	197 ± 1501	196 ± 148	259 ± 16	158 ± 142
RVEF (%)	31 ± 10	42 ± 10	34 ± 11	40 ± 10	33 ± 12	38 ± 10
RVEDV (ml)	235 ± 70	216 ± 86	208 ± 79	196 ± 74	187 ± 69	192 ± 70
RVESV (ml)	164 ± 62	128 ± 62	144 ± 68	122 ± 61	129 ± 65	121 ± 55
Mortality	Survivors (n=232)				Non-survivors (n=22)	
RVEF (%)	34 ± 11	41 ± 11			31 ± 13	36 ± 16
RVEDV (ml)	207 ± 71	195 ± 71			202 ± 79	207 ± 85
RVESV (ml)	141 ± 62	118 ± 56			144 ± 72	139 ± 75

Measurements were taken at baseline before treatment and at follow-up (12 ± 6 months). Improvement was defined as an increase of at least 47.5m in ISWT, a decrease of at least 6 points in E-10 score and one-year survival post-follow-up. Whereas worsening was defined as a reduction in ISWT of at least 47.5m, an increase of 6 points in E-10 score or mortality. Otherwise, patients were described as stable.

E-10, emPHasis-10 health-related quality of life questionnaire; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume

Supplemental Table 1: Change in RVEF at baseline and follow-up in treatment-naïve patients with PAH.

STUDY	*No. Patients*	*Follow-up (months)*	*Mean baseline RVEF*	*Mean follow-up RVEF*	*Mean difference [95% CI]*
Hassoun 2015	23	9	46	57	11 [6, 17]
Michelakis 2003	3	12	38	45	7 [-10, 24]
Peacock 2013	71	12	41	46	5 [0, 9]
Roeleveld 2004	10	12	34	38	4 [-7, 15]
Swift 2022*	16	12	32	37	5 [-3, 13]
Van de Veerdonk 2011	76	12	35	36	1 [-2, 4]
Van de Veerdonk 2017	45	12	36	40	4 [-1, 9]
van Wolferen 2006	15	12	33	39	6 [-9, 21]
Vonk Noordegraaf 2022	62	12	38	47	10 [5, 15]
Pooled mean	321	12	37	43	6 [3, 8]
ASPIRE	254	12	34	41	7 [5, 9]

* only treatment-naïve patients included in the analysis

Figures

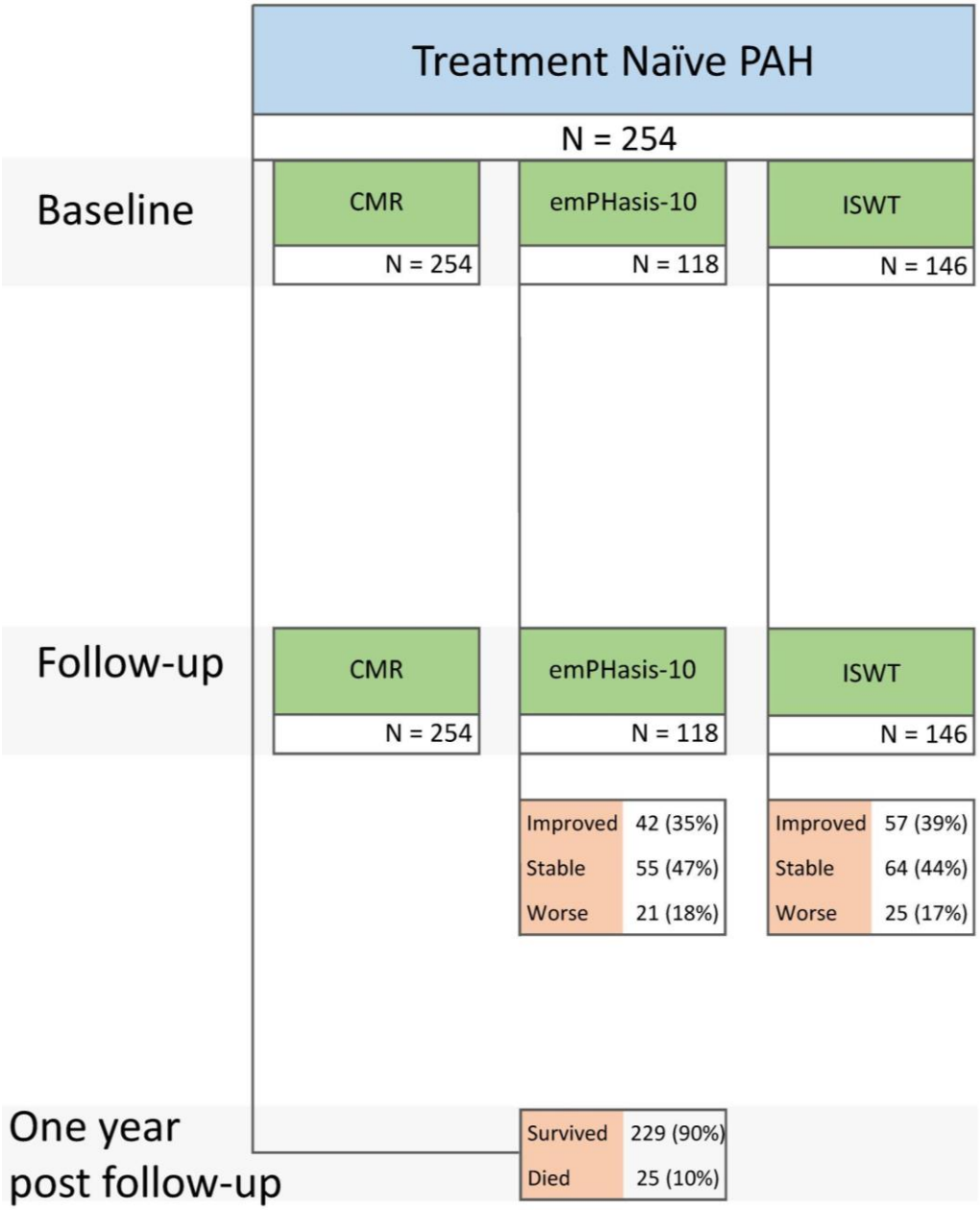

Figure 1: Patient flow chart

E-10; emPHasis-10 health-related quality of life questionnaire, ISWT; incremental shuttle walking test

1st CMR at baseline >>> 2nd CMR at 12±6 months >>> One-year follow-up.

E-10 and ISWT were performed mostly on the same day and within two weeks of CMR.

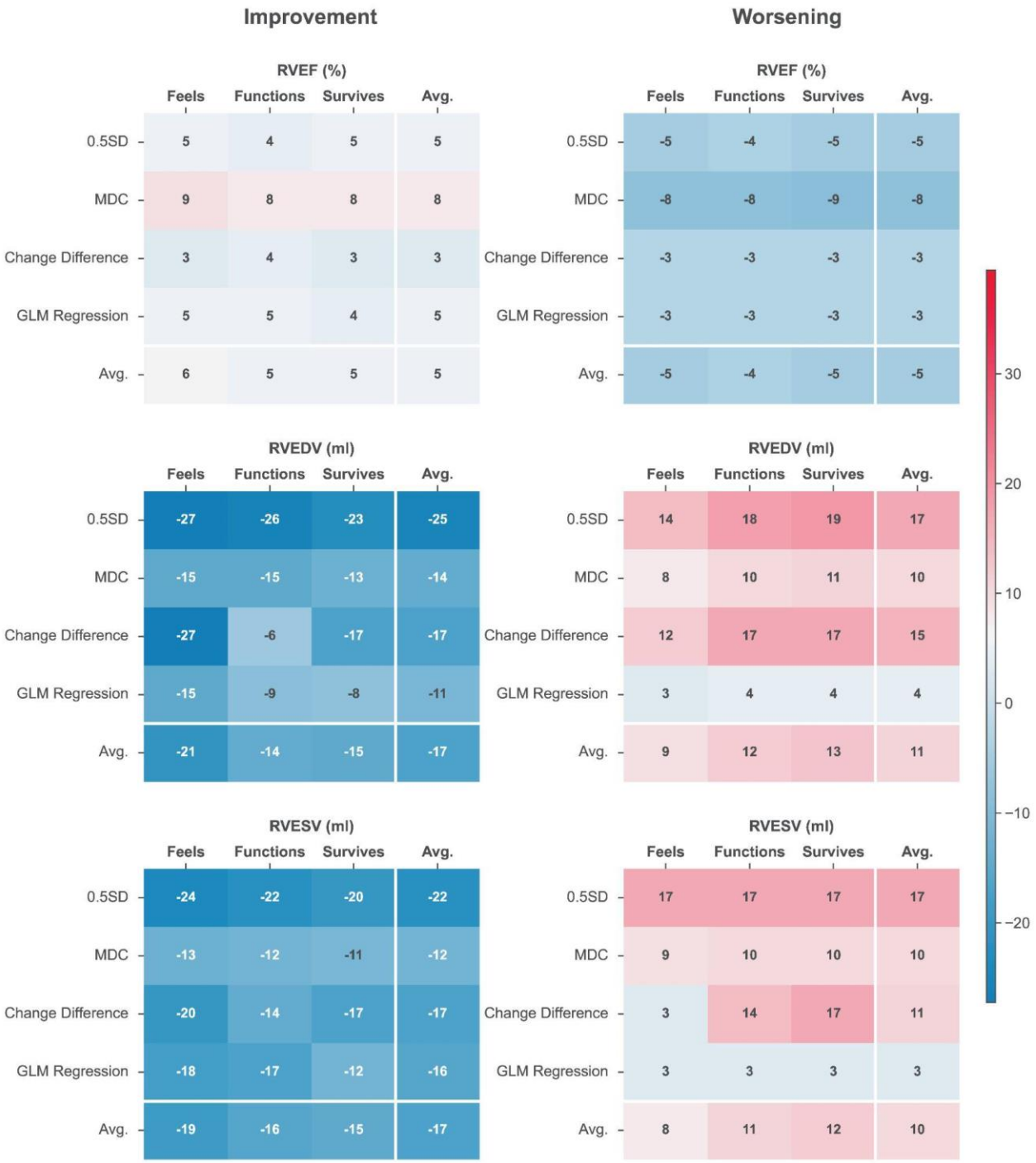

Figure 2: Heatmap of mean minimal important differences (MID) for improvement (left panel) and worsening (right panel) for absolute changes in right ventricular (RV) parameters. The heatmaps display the MIDs calculated using four different assessment methods: 0.5 standard deviation (SD), minimal detectable change (MDC), change difference, and general linear model (GLM) regression. The values are colour-coded, with blue representing lower MIDs and red representing higher MIDs. The bold white lines separate the average column and row for each parameter. RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.

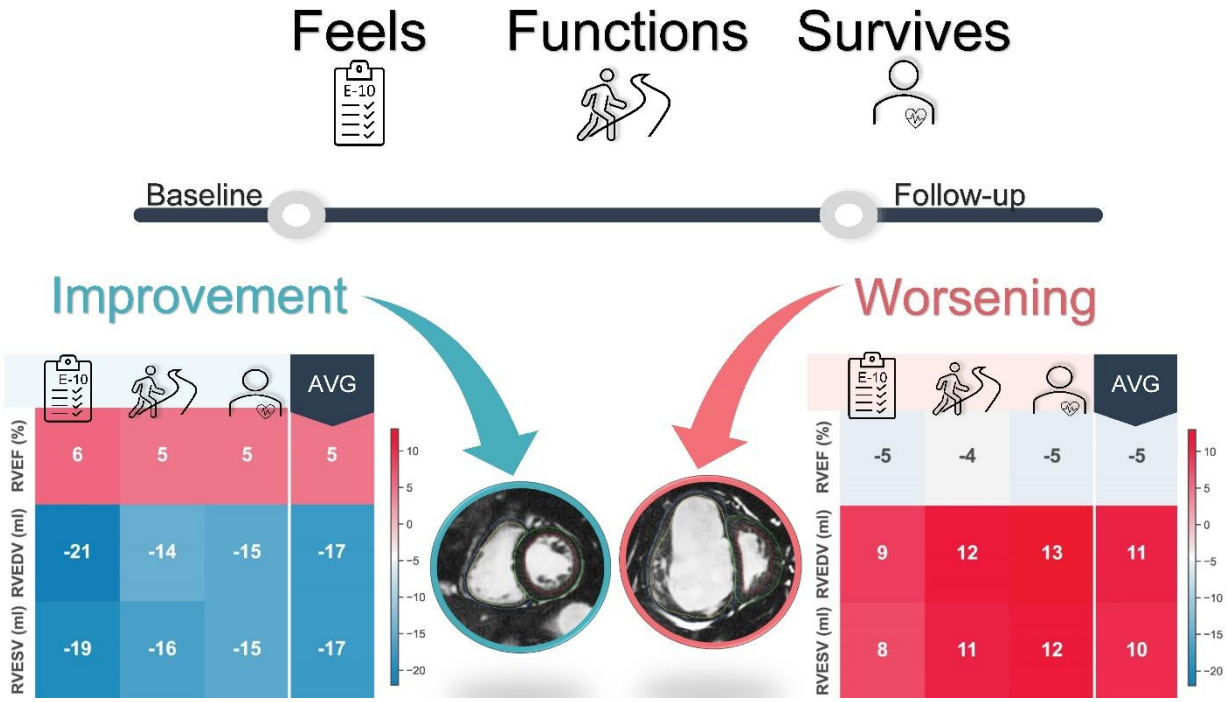

Figure 3: Summary of the CMR absolute change MIDs for how a patient "feels" benchmarked to emPHasis-10, "functions" benchmarked to Incremental Shuttle Walk Test or "survives" benchmarked to one-year mortality post-follow-up.

Lay Summary

Pulmonary arterial hypertension (PAH) is a disease of the vessels of the lung that causes their narrowing and stiffening. As a result, the heart pumping blood into these diseased lung vessels has to work harder and eventually gets worn out. PAH can affect patients' ability to function in daily activities and impact their quality of life. It also reduces their life expectancy dramatically. Patients are, therefore, often monitored and undergo several investigations to adapt treatment according to their situation. These investigations include a survey of how a patient feels (the emPHasis-10 questionnaire), functions (walking test) and how well the heart is coping with the disease (MRI of the heart).

Until now, it is unclear how changes on MRI of the heart reflect changes in how a patient feels and functions. Our study identified patients that had the emPHasis-10 questionnaire, walking test and MRI of the Heart at both the time of PAH diagnosis and one year later. This allowed us to compare how the changes in the different tests relate to each other. And because previous research identified thresholds for important changes in the emPHasis-10 questionnaire and the walking tests, we were able to use these tests as a benchmark for changes in the MRI of the heart.

Our study identified thresholds for change on heart MRI that might indicate whether a patient has improved or worsened. This finding might have implications for how patients are monitored in clinical practice and future research on PAH treatments.

Supplemental Table 1: Change in RVEF at baseline and follow-up in treatment naive patients with PAH

Study	*No. Patients*	*Follow-up (months)*	*Mean baseline RVEF*	*Mean follow-up RVEF*	*Mean difference [95% CI]*
Hassoun 2015	23	9	46	57	11 [6, 17]
Michelakis 2003	3	12	38	45	7 [-10, 24]
Peacock 2013	71	12	41	46	5 [0, 9]
Roeleveld 2004	10	12	34	38	4 [-7, 15]
Swift 2022*	16	12	32	37	5 [-3, 13]
Van de Veerdonk 2011	76	12	35	36	1 [-2, 4]
Van de Veerdonk 2017	45	12	36	40	4 [-1, 9]
van Wolferen 2006	15	12	33	39	6 [-9, 21]
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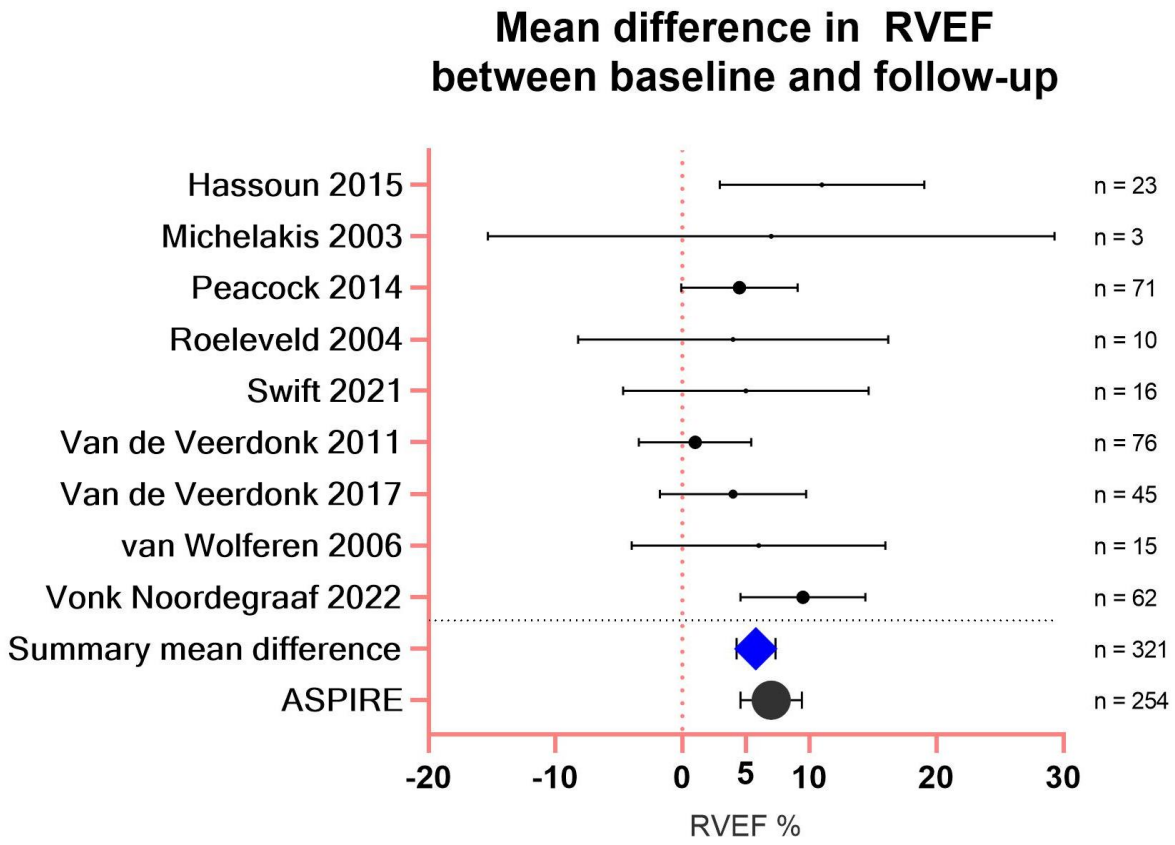
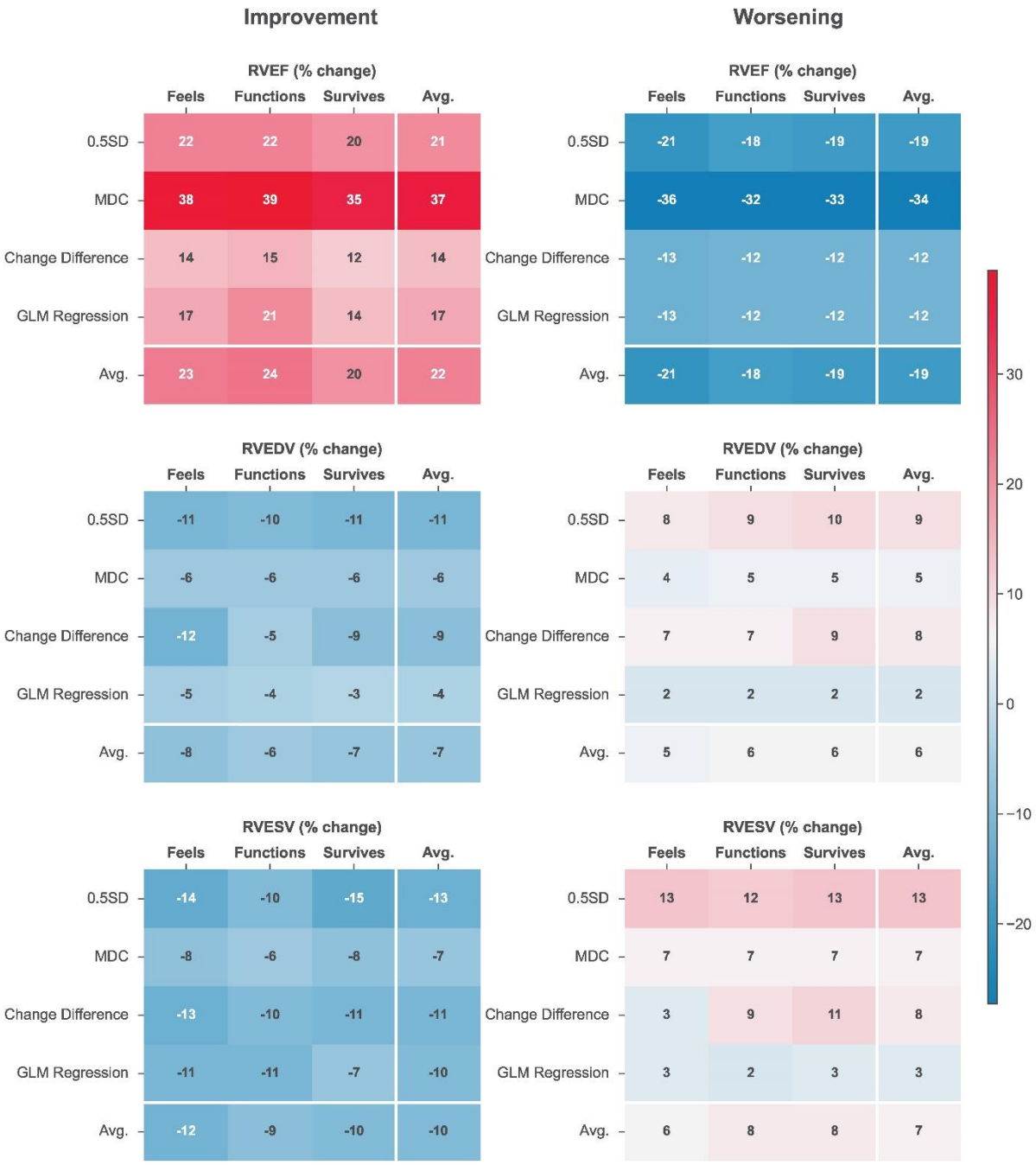
Pooled mean	321	12	37	43	6 [3, 8]
ASPIRE	254	12	34	41	7 [5, 9]

* only treatment naive patient included in the analysis



Supplemental Figure 1: Pooled summary of mean RVEF differences

Pooled differences of RVEF in treatment-naive PAH patients between baseline and 9-12 months follow-up post-treatment reported in nine studies. The pooled change (blue diamond) in RVEF was 6% (n = 321) compared to 7% in the current ASPIRE study (n= 254).



Supplemental Figure 2: Heatmap of mean minimal important differences (MID) for improvement (left panel) and worsening (right panel) for relative changes in right ventricular (RV) parameters expressed as change over baseline measurement x100. The heatmaps display the MIDs calculated using four different assessment methods: 0.5 standard deviation (SD), minimal detectable change (MDC), change difference, and

general linear model (GLM) regression. The values are colour-coded, with blue representing lower MIDs and red representing higher MIDs. The bold white lines separate the average column and row for each parameter.

RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.

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