SUPPLEMENTARY MATERIAL

Title: Effect of macitentan in pulmonary arterial hypertension and the relationship between echocardiography and cMRI variables: REPAIR echocardiography sub-study results

Authors: Adam Torbicki[1], Richard Channick[2], Nazzareno Galiè[3,4], David G Kiely[5,6], Pamela Moceri[7], Andrew Peacock[8], Andrew J Swift[6], Ahmed Tawakol[9], Anton Vonk Noordegraaf[10], Dayana Flores[11], Nicolas Martin[12], Stephan Rosenkranz[13]

Affiliations: [1]Department of Pulmonary Circulation, Thromboembolic Disease and Cardiology, Centre for Postgraduate Medical Education ECZ-Otwock, ERN-LUNG Member, Otwock, Poland; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Cardiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [4]Dipartimento DIMES, Università di Bologna, Bologna, Italy; [5]Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK; [6]National Institute for Health and Care Research Sheffield Biomedical Research Centre, Department of Infection, Immunity & Cardiovascular Disease, University of Sheffield, Sheffield, UK; [7]Cardiology Department, UR2CA, Pasteur University Hospital, Côte-d'Azur University, Nice, France; [8]Scottish Pulmonary Vascular Unit, Glasgow, UK; [9]Massachusetts General Hospital and Harvard Medical School, Boston, USA; [10]Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [11]Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, Global Medical Affairs, Allschwil, Switzerland; [12]Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, Statistical Decision Science, Allschwil, Switzerland; [13]Department of Cardiology, Heart Center, University Hospital Cologne, and Cologne Cardiovascular Research Center (CCRC), University of Cologne, Cologne, Germany.

Corresponding author: Adam Torbicki

Address: European Health Centre Otwock, F. Chopin Hospital, ul. Borowa 14/18, 05-400 Otwock, Poland

Email: atorbicki@gmail.com

Supplementary material

Table S1. List of Institutional Review Boards and Ethics Committees

Country	Site	Ethics Committee	Address	Central or local
Malaysia	9001	IJN Research Ethics Committee	National Heart Institute 145, Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia	Local
Singapore	1201, 1202*	NHG Domain Specific Review Board (DSRB)	Domain Specific Review Board (DSRB) c/o National Healthcare Group, NHG Group Research Nexus @One-North (South Tower), No. 3 Fusionopolis Link, #03-08, Singapore 138543	Local
Hong Kong	1301, 1302	Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)	Rm 901, 9/F, Administration Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong	Local
	1303	Research Ethics Committee (Kowloon Central/ Kowloon East Cluster) [REC (KC/KE)]	Rm 808, 8/F, Block S, Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong	Local
Russia	1101	Ethics Committee of Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation	2 Akkuratova street, St. Petersburg 197341	Local
	1102	Independent Ethics Committee of clinical trials of Federal State Budgetary Institution "National Medical Research Centre of Cardiology" of the Ministry of Health of the Russian Federation	3-d Cherepkovskaya street, 15a, Moscow, 121552	Local
Israel	8001	Ethics Helsinki Committee	Bait Shmuel Street 12 POB 3235, JERUSALEM zip: 91031, ISRAEL	Local
	8002	Ethics Helsinki Committee	Rager Blvd Beer-Sheva 85025, ISRAEL	Local
USA	1001*	Partners Human Research Committee	399 Revolution Drive Suite # 710 Somerville MA, 02145, US	Local
	1002*, 1004*, 1005,	Western Institutional Review Board	1019 39th Ave SE #120, Puyallup, WA 98374, US	Local

	1010*, 1014*			
	1006	UT Southwestern Institutional Review Board	5323 Harry Hines Blvd, Dallas, TX 75390, US	Local
	1007*	Aurora Health Care Research Subject Protection Program and IRB office	945 N. 12th Street P.O. Box 342 W310 Milwaukee, WI 53201-0342, US	Local
	1008*	Weill Cornell Medicine IRB	1300 York Ave. New York, NY 10065, US	Local
	1009*	University of Minnesota Human Research Protection Program	350-2 McNamara 200 Oak St. SE Minneapolis, MN 55414, US	Local
	1012	The Washington University in St Louis IRB	4590 Children's Place, Suite 2300 | St. Louis, MO 63110, US	Local
	1015*	Houston Methodist Research Institute IRB	6670 Bertner Ave, Houston, TX 77030, États-Unis	Local
Australia	2001*	The Prince Charles Hospital HREC	Building 14 Rode Road, Chermside QLD 4032 Australia	Central
France	(3002), (3003)* (3004)*, (3005), (3007), (3008), (3010)*, (3011)	Comité de Protection des Personnes Est III	Hôpital de Brabois. Rue du Morvan, 54500 Vandœuvre- lès-Nancy, France	Central
Germany	(4001), (4002)*, (4003), (4004)*, (4005), (4006)*, (4007), (4008)*	Ethic Committee of the Medical Faculty of Heidelberg	Alte Glockengießerei 11/1, 69115 Heidelberg, Germany	Central
Italy	5001*	Comitato Etico Azienda Ospedaliero Universitaria di Bologna Policlinico S.Orsola-Malpighi	Via Albertoni 15 40138 Bologna, Italy	Central
	5002	Comitato di Bioetica della Fondazione IRCCS Policlinico S. Matteo di Pavia	Viale Golgi, 19 27100 Pavia, Italy	Local

Netherlands	(6001), (6002), (6004), (6005)*, (6006)*	Medical Ethical Committee VU	De Boelelaan 1117 1081 HV Amsterdam, Netherlands	Central
United Kingdom	(7001)*, (7003), (7005)	NRES Committee Yorkshire & The Humber – Leeds West Health Research Authority	Jarrow REC Centre, Room 001, Jarrow Business Centre, Rolling Mill Road, Jarrow, Tyne and Wear. NE32 3DT, UK	Central

*Sites that were initiated but did not enrol any patients (if applicable)

Table S2. Change in additional echo variables from baseline to Weeks 26 and 52 (Echo subgroup, N = 45)

Echo variables	n	Baseline Mean (SD)	Change from baseline to Week 26 LS mean[a] (95% CL)	n	Change from baseline to Week 52 LS mean[a] (95% CL)
Tricuspid peak annular velocity, s', cm/s	27	9.7 (2.8)	2.1 (1.1, 3.0)	26	1.2 (0.4, 2.1)
RV ejection time[b], msec	32	283.0 (47.4)	26.2 (11.6, 40.7)	27	42.1 (22.9, 61.3)
RV ejection time[c], msec	28	274.7 (47.9)	14.5 (-1.6, 30.6)	27	23.1 (11.3, 34.9)
Total RV systolic time[b], msec	29	465.5 (54.2)	-13.7 (-30.3, 2.9)	25	-9.2 (-34.3, 16.0)
Total RV systolic time[c], msec	28	453.0 (73.8)	0.5 (-16.2, 17.2)	27	14.1 (-6.1, 34.3)
LV stroke volume index, mL/m^2	29	28.9 (9.9)	5.3 (2.2, 8.4)	25	6.8 (3.1, 10.5)
Cardiac output[d], L/min	29	3.7 (1.1)	0.47 (0.07, 0.88)	25	0.64 (0.25, 1.04)
RV Myocardial Performance Index[c]	28	0.66 (0.22)	-0.08 (-0.16, <0.01)	27	-0.09 (-0.18, 0.01)
Mitral peak E-wave velocity, cm/s	36	57.1 (17.0)	10.6 (4.5, 16.6)	32	18.0 (11.4, 24.6)
Mitral peak A-wave velocity, cm/s	35	62.7 (19.1)	-0.06 (-5.0, 4.9)	32	-0.14 (-4.7, 4.4)
Mitral E/E' ratio	29	6.07 (2.81)	0.16 (-0.80, 1.12)	30	0.31 (-0.30, 0.91)
Mitral annulus peak early diastolic velocity, e', cm/s	30	10.2 (3.8)	2.1 (1.1, 3.0)	31	1.9 (1.0, 2.8)
RV end-diastolic area, cm^2	42	28.1 (6.3)	-1.7 (-3.2, -0.2)	38	-2.5 (-4.0, -1.0)
RV end-systolic area, cm^2	42	21.3 (7.0)	-3.2 (-4.9, -1.6)	38	-3.6 (-5.0, -2.2)
LV end-systolic volume, mL	32	23.9 (11.0)	5.2 (2.2, 8.3)	31	2.6 (-0.62, 5.9)
LV eccentricity index, end-diastole	34	1.4 (0.31)	-0.03 (-0.15, 0.09)	27	-0.03 (-0.14, 0.07)
LV eccentricity index, end-systole	34	1.7 (0.54)	-0.16 (-0.32, 0.01)	28	-0.02 (-0.24, 0.20)
RV acceleration time[b], msec	31	79.6 (25.8)	8.6 (-1.1, 18.3)	26	17.6 (7.2, 28.0)

RV acceleration time[c], msec	25	83.0 (25.3)	-10.4 (-18.8, -2.0)	23	-4.3 (-15.3, 6.8)
Pericardial effusion size	43	0.42 (0.63)	-0.14 (-0.25, -0.04)	38	-0.13 (-0.25, -0.01)

[a]Analyzed using an ANCOVA with a factor for PAH background therapy and a covariate for baseline parameter value. [b]By pulsed wave doppler. [c]By tissue doppler. [d]Determined from LV outflow tract. ANCOVA: analysis of covariance; CL: confidence limit; echo: echocardiography; LS: least squares; LV; left ventricular; PJV: peak jet velocity; RV: right ventricular; SD: standard deviation.

Table S3. Change in cMRI variables from baseline to Weeks 26 and 52 (Safety set, N = 87)

cMRI variables	n	Baseline Mean (SD)	Change from baseline to Week 26[a] LS Mean (95% CL)	n	Baseline Mean (SD)	Change from baseline to Week 52[a] LS Mean (95% CL)
RV stroke volume by flow[b], mL	73	52.1 (17.8)	11.6 (8.1, 15.1)[c]	68	51.9 (17.8)	12.7 (9.3, 16.2)
RV stroke volume by volume[d], mL	78	58.5 (20.7)	10.0 (6.0, 13.9)	72	59.0 (21.2)	13.0 (8.9, 17.0)
RVEDV, mL	78	148.4 (47.8)	-6.2 (-12.5, 0.1)	72	148.0 (46.2)	-5.4 (-11.7, 0.8)
RVESV, mL	78	90.0 (40.9)	-16.4 (-20.6, -12.2)	72	89.0 (38.4)	-18.7 (-23.6, -13.8)
RV ejection fraction by flow[b], %	72	37.8 (15.0)	10.1 (7.5, 12.8)	67	37.6 (15.0)	10.0 (7.5, 12.5)
RV ejection fraction by volume[d], %	78	41.2 (12.8)	8.5 (6.8, 10.2)	72	41.5 (12.6)	10.5 (8.3, 12.6)
RV mass, g	78	110.6 (46.8)	-10.1 (-13.8, -6.4)	72	111.2 (47.8)	-8.8 (-13.1, -4.6)
LV stroke volume by flow[e], mL	71	47.2 (14.8)	13.4 (10.5, 16.4)	67	47.5 (15.5)	14.0 (11.0, 16.9)
LV stroke volume by volume[d], mL	78	54.2 (17.6)	15.5 (12.2, 18.8)	72	54.9 (18.4)	14.6 (11.5, 17.6)
LVEDV, mL	78	86.1 (28.2)	16.9 (12.2, 21.5)	72	87.4 (29.1)	16.6 (12.6, 20.6)
LVESV, mL	78	31.9 (16.0)	1.4 (-1.1, 3.9)	72	32.4 (15.8)	2.1 (-0.3, 4.5)
LV ejection fraction by flow[e], %	70	56.1 (11.5)	3.5 (1.1, 5.9)	67	55.7 (11.3)	5.0 (2.7, 7.3)
LV ejection fraction by volume[d], %	78	64.0 (10.9)	4.5 (3.0, 6.0)	72	63.8 (10.6)	4.0 (2.4, 5.6)
LV mass, g	78	103.5 (24.3)	3.7 (1.5, 6.0)	72	104.4 (25.8)	4.1 (1.5, 6.7)
RVEDV / LVEDV[f]	78	1.80 (0.66)	0.79 (0.76, 0.83)[g]	72	1.80 (0.65)	0.80 (0.77, 0.84)[g]
RVESV / LVESV[f]	78	3.20 (1.71)	0.78 (0.73, 0.83)[g]	72	3.20 (1.73)	0.73 (0.67, 0.80)[g]

[a]Analyzed using an ANCOVA with a factor for PAH background therapy and a covariate for baseline. [b]Determined from pulmonary artery flow. [c]96% CL. [d]Determined from volume. [e]Determined from aortic flow. [f]Log transformed. [g]Geometric mean ratio of week 26[a] to baseline (95% CL). ANCOVA: analysis of covariance; CL: confidence limit; cMRI: cardiac magnetic resonance imaging; LS: least squares; LV: left ventricular; LVEDV: LV end-diastolic volume; LVESV: LV end-systolic volume; PAH: pulmonary arterial hypertension; RV: right ventricular; RVEDV: RV end-diastolic volume; RVESV: RV end-systolic volume; SD: standard deviation.

Table S4. Changes in RHC variables and functional parameters from baseline to Week 26 and Week 52 (Safety set, N = 87)

RHC parameters						
	n	**Baseline** Mean (SD)	**Change from baseline to Week 26[a]** LS Mean (95% CL)			
PVR (dyn.sec/cm^5)	80	984.7 (669.1)	-376.2 (-466.3, -286.1)[b]			
mPAP (mmHg)	80	53.5 (15.2)	-7.9 (-10.1, -5.8)			
mRAP (mmHg)	79	6.8 (4.2)	-0.5 (-1.2, 0.3)			
Cardiac index (L/min/m^2)	80	2.4 (0.7)	0.5 (0.4, 0.7)			
Functional parameters						
	n	**Baseline** Mean (SD)	**Change from baseline to Week 26[a]** LS Mean (95% CL)	**n**	**Baseline** Mean (SD)	**Change from baseline to Week 52[a]** LS Mean (95% CL)
6MWD (m)	83	405.3 (116.7)	38.9 (24.2, 53.5)	76	406.8 (118.4)	40.5 (22.5, 58.5)
	n	**Baseline** Mean (SD)	**Geometric mean ratio of Week 26[a] to baseline** (95% CL)	**n**	**Baseline** Mean (SD)	**Geometric mean ratio of Week 52[a] to baseline** (95% CL)
NTproBNP (ng/L)	72	1172.8 (1824.0)	0.4 (0.4, 0.5)	68	1210.9 (2019.2)	0.4 (0.4, 0.5)

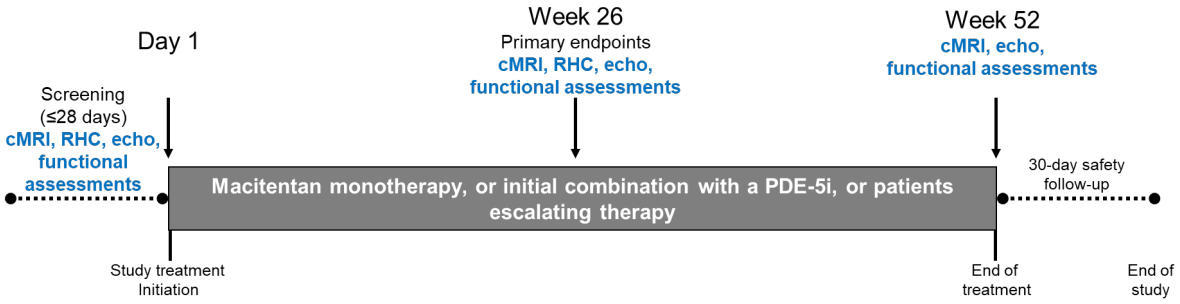
[a]Analyzed using an ANCOVA with a factor for PAH background therapy and a covariate for baseline value. [b]Change from baseline to Week 26[a] Mean (95% CL).
6MWD: 6-minute walk distance; ANCOVA: analysis of covariance; CL: confidence limit; LS: least squares; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; NTproBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterization; SD: standard deviation.

Table S5. Exposure and overview of safety (Echo subgroup, N = 45)

	Echo subgroup (N = 45)
Duration of study treatment (weeks)	
Mean (SD)	48.2 (10.9)
Median (Min, Max)	51.9 (5.4, 54.7)
AEs and SAEs	
Patients with ≥1 treatment-emergent AE (≥10% of patients), n (%)	39 (86.7)
Peripheral edema	12 (26.7)
Headache	11 (24.4)
Dizziness	9 (20.0)
Cough	7 (15.6)
Diarrhea	7 (15.6)
Myalgia	7 (15.6)
Nasopharyngitis	6 (13.3)
Back pain	5 (11.1)
Nasal congestion	5 (11.1)
Patients with ≥1 AE leading to discontinuation of study treatment by Preferred Term, n (%)	5 (11.1)
Increased aspartate aminotransferase	2 (4.4)
Increased liver function test	1 (2.2)
Peripheral edema	1 (2.2)
Increased transaminases	1 (2.2)
Patients with ≥1 treatment-emergent SAE, n (%)	5 (11.1)
Fatal treatment-emergent SAE	0

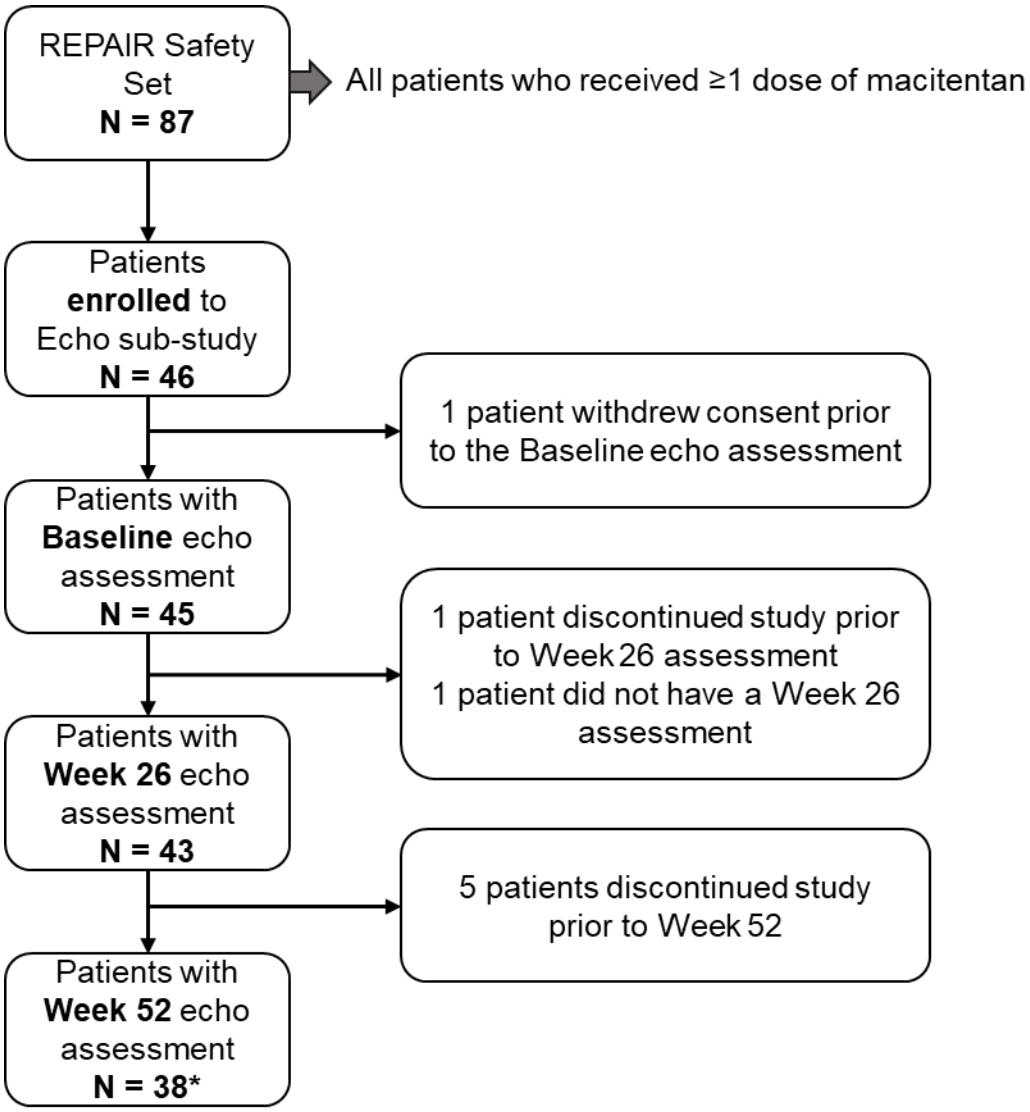
Preferred Terms are based on MedDRA version 22.0. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; AE: adverse event; echo: echocardiography; SAE: serious AE; SD: standard deviation.

Figure S1. Study design



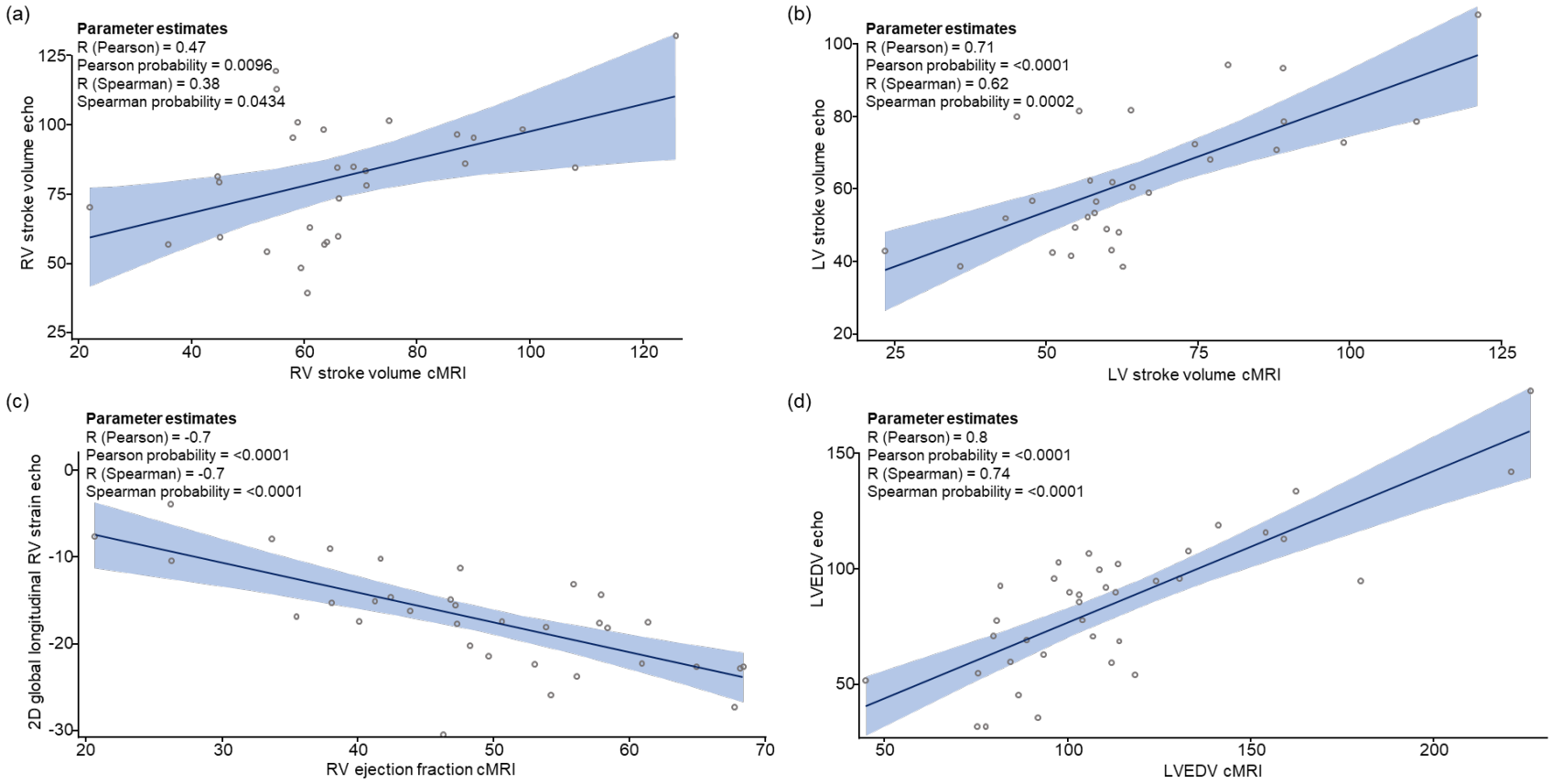
Study design figure adapted from the previously published article [1]. Physicians' choice of treatment strategy, macitentan (10 mg) initiated: in treatment-naïve patients; in patients receiving stable background PDE-5i; in treatment-naïve patients as initial combination with a PDE-5i. cMRI: cardiac magnetic resonance imaging; echo: echocardiography; PDE-5i: phosphodiesterase type 5 inhibitor; RHC: right heart catheterization.

Figure S2. Patient disposition



*Includes one patient who did not have a Week 26 echo assessment performed. Echo: echocardiography.

Figure S3. Correlation analysis of (a) RV stroke volume echo *versus* RV stroke volume cMRI (N = 29), (b) LV stroke volume echo *versus* LV stroke volume cMRI (N = 30), (c) 2D global longitudinal RV strain echo *versus* RV ejection fraction by volume cMRI (N = 35), (d) LVEDV echo *versus* LVEDV cMRI (N = 37), at Week 26 (Echo subgroup, N = 45)



The bands show the 95% confidence limits. cMRI: cardiac magnetic resonance imaging; echo: echocardiography; LV: left ventricular; LVEDV: LV end-diastolic volume; RV: right ventricular.

References

1. Vonk Noordegraaf A, Channick R, Cottreel E, Kiely DG, Marcus JT, Martin N, et al. The REPAIR Study: Effects of Macitentan on RV Structure and Function in Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2022;15:240–53. doi:10.1016/j.jcmg.2021.07.027.