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ORIGINAL ARTICLE

Adherence to heart failure treatment in patients with peripartum cardiomyopathy

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Abstract

Aims Peripartum cardiomyopathy (PPCM) is characterized by left ventricular (LV) dysfunction developing towards the end of pregnancy or in the first months postpartum. Although about 60% of women with PPCM (the majority of which are prescribed evidence based heart failure [HF] medications) show LV recovery within 6 to 12 months, others remain with persistently impaired LV function. Poor adherence to medical therapy represents a major cause of avoidable hospitalizations, disability, and death in other cardiovascular conditions. In this study, we aimed to determine drug adherence to HF therapy among women with PPCM and to identify possible associations between drug adherence and LV recovery, functional status and psychological well-being.

Methods and results In this single-centre, prospective, observational study, we included 36 consecutive women with PPCM. Adherence to HF treatment was assessed by (i) verifying the collection of pharmacy refills and (ii) using liquid chromatography high-resolution mass spectrometry (LC-HRMS). Participants were thereby classified as 'adherent' (i.e. all prescribed HF drugs were detectable by LC-HRMS), 'partially adherent' (i.e. at least one prescribed drug detectable) or 'non-adherent' (i.e. none of the prescribed drugs detectable). Health state index scores were assessed by EQ-5D-5L and HADS-A/D (for anxiety/depression). Patients' median age was 32.4 years (IQR 27.6–36.1). At the adherence visit (which occurred at a median of 16 months [IQR 5–45] after PPCM diagnosis), prescription included beta-blockers (77.8%), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (75%), mineralocorticoid receptor antagonists (47.2%) and loop diuretics (95.2%). Less than two thirds of patients (63.9%) collected all their pharmacy refills in the 6 months prior to adherence visit. According to LC-HRMS, 23.5% participants were classified as adherent, 53.0% as partially adherent, and 23.5% as non-adherent. Adherence was associated with significantly lower LVEDD at follow-up (47 mm [IQR 46–52), vs. 56 mm [IQR 49–64] with partial adherence, and 62 mm [IQR 55–64] with non-adherence, $P = 0.022$), and higher LVEF at follow-up (60% [IQR 41–65]), vs. partially adherence (46% [IQR 34–50]) and non-adherence (41.0% [IQR 29–47], $P = 014$). Adherent patients had a lower overall EQ- 5D score (5.5 [IQR 5–7.5], vs. 6 [IQR 5–7] in partially adherent, and 10 [IQR 8–15] in non-adherent patients, $P = 0.032$) suggestive of a better self-rated health status.

Conclusions Adherence to HF therapy was associated with favourable LV reverse remodelling in PPCM and better self-rated health status. Our study highlights the importance of drug adherence for functional recovery. Drug adherence should be an important component of patient communication and specific interventions in PPCM.

Keywords Liquid chromatography; LV reverse remodelling; Mass spectrometry; Medication adherence; Peripartum cardiomyopathy; Risk stratification

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Introduction

Peripartum cardiomyopathy (PPCM) is a pregnancy-associated form of heart failure, which occurs towards the end of pregnancy or in the months following delivery.[1] The disease is defined as new-onset left ventricular (LV) systolic dysfunction (i.e. LV ejection fraction [LVEF] ≤ 45% at time of presentation), in the absence of any pre-existing heart disease.[1] PPCM is a major cause for maternal morbidity and mortality worldwide.[2] A recent meta-analysis revealed a global all-cause mortality rate of 9.8%, and 58.7% of patients exhibiting left ventricular recovery within a 12-month period. However, major regional variations were present. A sub-analysis suggested that a frequent prescription (≥80%) of beta-blockers and angiotensin-converting-enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARBs) was associated with significantly reduced all-cause mortality at 6 months, and significantly lower all-cause mortality and better LV recovery at 12 months, respectively.[3]

In other forms of HF, poor adherence to evidence-based medications is a major cause of avoidable hospitalizations, disability, and death.[4–6] However, to the best of our knowledge, no prior study has objectively investigated adherence rates to HF therapy in PPCM. As a potentially reversible condition, medical treatment is of great importance for subsequent LV recovery in PPCM. However, it still needs to be elucidated whether poor adherence contributes to LV-non-recovery in PPCM.

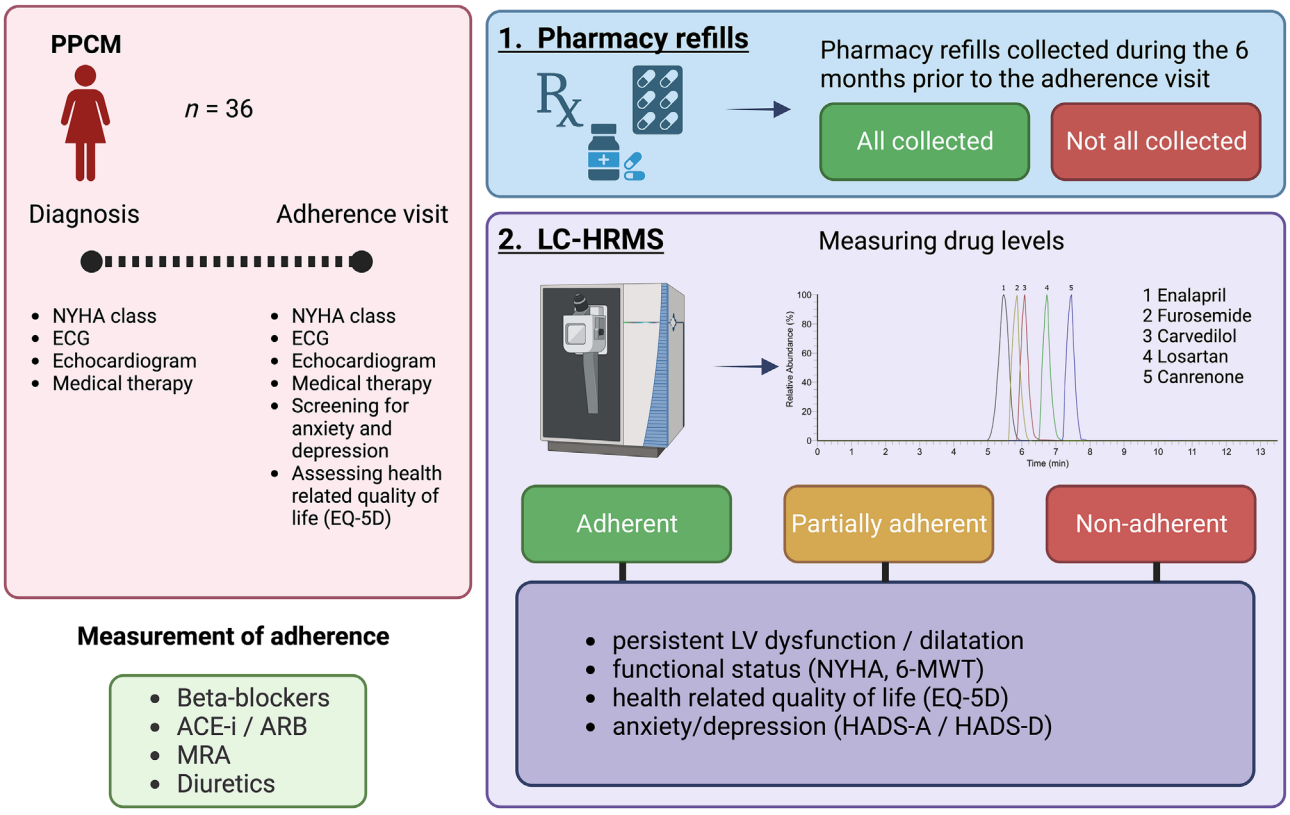
In this study, we aimed to further our understanding on drug adherence rates in PPCM and to assess potential associations between LV remodelling, functional status, and psychological well-being among patients with PPCM.

Methods

Study design

Groote Schuur Hospital (GSH) is a tertiary academic hospital affiliated to the University of Cape Town (UCT) and is a referral centre for patients with cardiomyopathy.[7] At time of diagnosis, all consecutive, consenting patients with PPCM are enrolled to a dedicated PPCM registry, and return for regular outpatient follow-up visits.[8] In this prospective, single-centre study, we invited all patients who attended their scheduled out-patient follow-up appointments to take part in this sub-study on drug adherence (*Figure 1*).

Figure 1 Study design including recruitment, data collection and assessment of adherence.



The primary objective was to assess the adherence to medication prescribed for PPCM. Drug adherence was measured by (i) establishing whether patients collected all their pharmacy refills in the months the 6 months prior to the adherence visit and (ii) by measuring drug levels in plasma. The latter was objectively performed by using liquid chromatography high-resolution mass spectrometry (LC-HRMS). The secondary objective was to determine whether drug adherence was associated with myocardial recovery, functional status, quality of life, anxiety and depression. Ethical approval was obtained from the Human Research Ethics Committee (HREC) at UCT (HREC Ref. 308/2021). The study was performed in accordance with the Declaration of Helsinki and all patients provided written informed consent prior to study inclusion.

Baseline data, including age, medical and obstetric history, clinical presentation (including New York Heart Association [NYHA] functional class [FC]), 12-lead ECG, and transthoracic echocardiogram were recorded at time of first presentation (i.e. PPCM diagnosis) as well as on the day of the adherence visit (i.e. follow-up visit).

Knowledge about prescribed drugs and collection of pharmacy refills

We assessed all prescribed medication, and the patients' knowledge thereof, by means of a questionnaire on the day of the adherence visit. Patients were asked to indicate the frequency of drug interruptions. Their pharmacy refills were verified through the provincial pharmacy record, which documents whether prescribed drugs were collected from their dedicated, local pharmacies, in the 6 months prior to the adherence visit or not.

None of the patients included were pregnant or were planning a subsequent pregnancy. Therefore, discontinuation of HFrEF therapy would not have been indicated.

Drug adherence analysis by liquid chromatography high-resolution mass spectrometry

Ethylenediamine tetraacetic acid (EDTA) blood was drawn at the adherence visit, immediately centrifuged and the supernatant was separated. The plasma samples were stored at −80°C before being analysed at the Department of Experimental and Clinical Toxicology at Saarland University (Homburg/Saar, Germany). In brief, human plasma (100 μL) was prepared according to Helfer et al.[9] by precipitation with 200 μL of acetonitrile (0.1% formic acid). After shaking and centrifugation (15 000× *g*, 30 min), the supernatant was transferred into an LC vial and injected onto the LC-HRMS system. A Thermo Fisher Scientific (TF, Dreieich, Germany) Dionex UltiMate 3000 RS pump consisting of a degasser, a quaternary pump, and an Ultimate Autosampler, coupled with a TF Q Exactive Plus equipped with a heated electrospray ionization (HESI)-II source was used. Gradient reversed-phase elution was performed on a Thermo Fisher Scientific (TF) Accucore Phenyl-Hexyl column (100 mm × 2.1 mm, 2.6 μm). The mobile phase consisted of 2 mM aqueous ammonium formate containing acetonitrile (1%, v/v) and formic acid (0.1%, v/v, pH 3, eluent A), as well as 2 mM ammonium formate solution with acetonitrile:methanol (1:1, v/v) containing water (1%, v/v) and formic acid (0.1%, v/v, eluent B). For separation of the analytes, the following gradient was used: 0–1 min 1% B, 1–10 min to 99% B, 10–11.5 min hold 99% B, and 11.5–13.5 min hold 1% B, at a flow rate of 0.5 mL/min from 0 to 10 min and 0.8 mL/min from 10 to 13.5 min. Mass spectrometric analysis was performed in positive or negative full-scan mode and data-dependent MS2 (dd-MS2) with priority to mass-to-charge ratios (m/z) of parent compounds (inclusion list). HESI-II source conditions were as follows: ionization mode, positive or negative; sheath gas, 60 AU; auxiliary gas, 10 AU; sweep gas, 3 AU; spray voltage, 3.5 kV in positive and −4.0 kV in negative mode; heater temperature 320°C; ion transfer capillary temperature, 320°C; and S-lens RF level, 50.0. For identification of the analytes and examination of the chromatographic separation TF Xcalibur Qual Browser software version 4.1 was used.

Definition of adherence

There is no universal definition of adherence (i.e. to classify whether patients are adherent to their prescribed drugs or not), even though a framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials that has recently been published.[10] In our study, we determined drug adherence by verifying pharmacy refills and by measuring plasma drug levels by means of LC-HRMS:

- For pharmacy refills, patients were classified as adherent if they collected all prescriptions in the 6 months prior to the adherence visit, and non-adherent if they missed one or more collections.
- Based on LC-HRMS measurements, we classified participants as 'adherent' if all prescribed HF drugs (i.e. beta-blocker, ACE-i/ARBs, and mineralocorticoid receptor antagonists [MRA]) were detectable in the patient's plasma and were within therapeutic target range. Patients were classified as 'partially adherent', if at least one prescribed drug was detectable in plasma and within therapeutic target range. 'Non-adherence' was defined if none of the prescribed HF drugs were detectable in the plasma.

Outcomes

LV recovery was defined as LVEF ≥ 50% at the adherence visit, whereas LV reverse remodelling was defined as LVEDD ≤ 52 mm. These echocardiographic measurements were performed according to the current American Society of Echocardiography recommendations.[11]

The participants' self-rated health was assessed at the adherence visit using the EQ-5D-5L™-score developed by the EuroQol Research Foundation©. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

A validated hospital anxiety and depression scale (HADS-A/D) was used as a screening tool for underlying anxiety and depression at the time of the adherence visit. The self-rated questionnaire consists of seven statements on each disorder with a four-point rating scale with an overall score ranging between 0 and 21 for depression and anxiety. A score of ≥11 is considered a clinically significant disorder, whereas a score between 8 and 10 suggests milder form.[12] A cut-off score of ≥8 has been shown to have the highest best sensitivity and specificity to indicate possible underlying anxiety and depression.[13]

Statistical analysis

Data were captured using a case report form (CRF) on Research Electronic Data Capture (REDCap),[14] a secure online database manager hosted at the University of Cape Town. Stata (Version 17, StataCorp, College Station, TX, USA) and Graphpad Prism (Version 9.5.1; GraphPad Software, San Diego, CA, USA) were used for statistical analysis. Normality of data was tested by using the Kolmogorov–Smirnov or Shapiro–Wilk test. Continuous variables were summarized as means with standard deviations (SD) for parametric data or median with interquartile range (IQR) for non-parametric data. Categorical variables were expressed as frequencies and percentages. The chi-square test or the Fisher exact test was used to compare dichotomous data. The unpaired Student t test (when normally distributed) or Mann–Whitney *U* test (for nonparametric data) was used to compare continuous variables. Comparisons between baseline data and the adherence visit as well as between adherence categories ('adherent', 'partially adherent', or 'non-adherent') were made as appropriate. A *P* value of <0.05 was considered to indicate statistical significance.

Results

This study included 36 patients with a median age of 32.4 years (IQR 27.6–36.1) (*Table 1*). The median time between the first presentation (i.e. PPCM diagnosis) and the adherence visit was 16 months (IQR 5–45).

At the time of diagnosis, about 80% of patients presented with severe symptoms of HF (NYHA FC III/IV). Echocardiography demonstrated a median LV end-diastolic dimensions (LVEDD) of 59.5 mm (IQR 55–67) and a median LVEF of 31%

Table 1 Patients' characteristics at baseline and adherence visit

	Baseline visit (time of PPCM diagnosis) Total *N* = 36	Follow-up visit (adherence assessed) Total *N* = 36	*P*-value
Age at presentation (years)	32.4 (27.6–36.1)		
Time between visits (months)		16 (5–45)	
Parity	2.0 (1.0–3.0)		
NYHA FC			0.799
I	0	29 (80.6)	
II	7/33 (21.2)	2 (5.6)	
III	16/33 (48.5)	5 (13.9)	
IV	10/33 (30.3)	0	
SBP (mmHg)	118.0 (102.0–131.0)	121.0 (115.0–134.0)	0.090
DBP (mmHg)	70.0 (66.0–82.0)	70.0 (62.0–87.0)	0.925
Heart rate (b.p.m.)	93.0 (80.0–109.0)	73.5 (66.0–85.0)	0.001
LVEDD (mm)	59.5 (55.0–67.0)	55.0 (48.0–62.0)	0.079
LVESD (mm)	52.5 (47.0–57.0)	42.0 (34.0–51.0)	0.011
LVEF (%)	31.0 (23.0–38.0)	47.0 (34.0–55.0)	<0.001
Beta-blocker	30/31 (96.8)	28 (77.8)	0.012
ACE-i/ARB	29 (80.6)	27 (75.0)	0.535
MRA	16/20 (80.0)	17 (47.2)	0.030
Loop diuretics	27/30 (90.0)	20/21 (95.2)	0.578
Bromocriptine	14/16 (87.5)	-	

Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.
ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DBP, diastolic blood pressure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA FC, New York Heart Association functional class; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.

(IQR 23–38). Prescription at discharge from hospital included beta-blockers (96.8%), ACE-i/ARB (80.6%), MRA (80%), loop diuretics (90%) and bromocriptine (87.5%).

At the adherence visit, the majority of patients did not report any symptoms of heart failure (80.6% classified as NYHA FC I). On echocardiography, the median LVEDD and LVEF had improved to 55 mm (IQR 48–62, $P = 0.079$) and 47% (IQR 34–55, $P < 0.001$), respectively. The average heart rate decreased significantly between the two visits (93 bpm [IQR 80–109] vs. 73.5 [IQR 66–85], $P = 0.001$). At the adherence visit, drug prescription consisted of beta-blockers (77.8%), ACE-i/ARB (75%), MRA (47.2%) and loop diuretics (95.2%).

Table 2 Psychosocial characteristics at the adherence visit

	Total ($N = 36$)
How far do you stay from your nearest pharmacy?	
Walking distance	12 (33.3)
Travel by own car	2 (5.6)
Public transport	22 (61.1)
Who collects your medication?	
Self	31 (86.1)
Family member	4 (11.1)
Home delivery	1 (2.8)
Do you have any reminders to take your medication?	
Cell phone	7 (19.4)
Pill box	2 (5.6)
Family member	2 (5.6)
None	24 (66.7)
Medication plan	1 (2.8)
Have you ever interrupted your treatment?	11 (30.6)
Reason for interruption	
Side-effect	1/10 (10.0)
Not enough medication	5/10 (50.0)
Did not think it was necessary	4/10 (40.0)
Pharmacy refills (in 6 months prior to follow up visit)	
Not all collected	13 (36.1)
All collected	23 (63.9)
Adherence by measured drug levels	
Non-adherent	6/34 (23.5)
Partially adherent	18/34 (52.9)
Adherent	8/34 (23.5)

Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.

The majority of patients in this cohort collected their medication themselves (86.1%) and relied on public transport to reach their nearest pharmacy (61.1%). As elaborated in *Table 2*, few patients used reminders to take their medication. Almost one third of the cohort (30.6%) admitted having interrupted their treatment, mostly because they did not have enough medication at home (50%) and did not collect in time, or did not think it was necessary anymore (40%). Less than two thirds of patients (63.9%) collected all their pharmacy refills in the 6 months prior to adherence visit.

As illustrated in *Figure 2*, 85.7% of patients who were prescribed HF treatment knew the beta-blocker name, 81.5% knew the ACE-i/ARB name, 79.9% knew the MRA name, and 95.0% knew the diuretic name.

Assessment of adherence using liquid chromatography high-resolution mass spectrometry

Based on detectable drug levels measured by LC-HRMS, 23.5% participants were classified as adherent, 53.0% as partially adherent, and 23.5% as non-adherent to HF therapy. Notably, patients who did not collect all their pharmacy refills were more likely to have undetectable drug levels ($P < 0.001$) (*Figure 3*).

The functional status (as measured by NYHA FC and 6-min walk test) did not differ between patients who were classified as being adherent, partially adherent and non-adherent. Adherent patients tended to have a lower systolic (112 mmHg [IQR 102–123] vs. partially adherent (119 mmHg [IQR 112.5–137.5] and non-adherent patients 132 mmHg [IQR 119–140.5], $P = 0.077$), and diastolic blood pressure (64 mmHg [IQR 52–69] vs. partially adherent (70 mmHg [IQR 60–84.5] and non-adherent patients 85 mmHg [IQR 68–90], $P = 0.071$).

Importantly, adherence was associated with better LV reverse remodelling at the adherence visit. Patients classified as adherent had significantly smaller LVEDD (47 mm [IQR

Figure 2 Detected drug levels in plasma as assessed by liquid chromatography high-resolution mass spectrometry (LC-HRMS), patients' knowledge of drug name, dose and frequency. ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist.

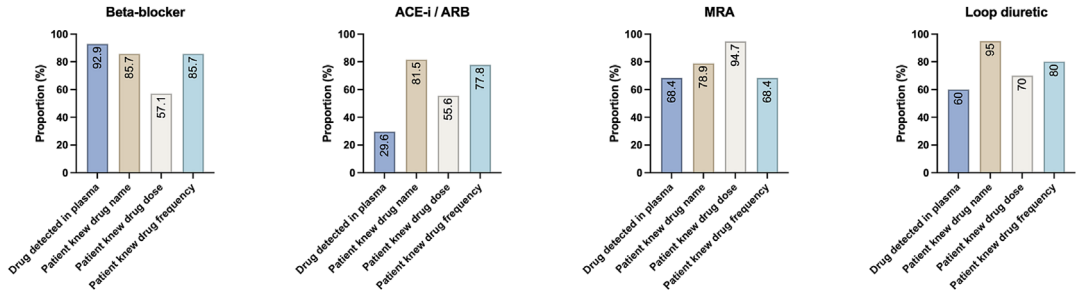
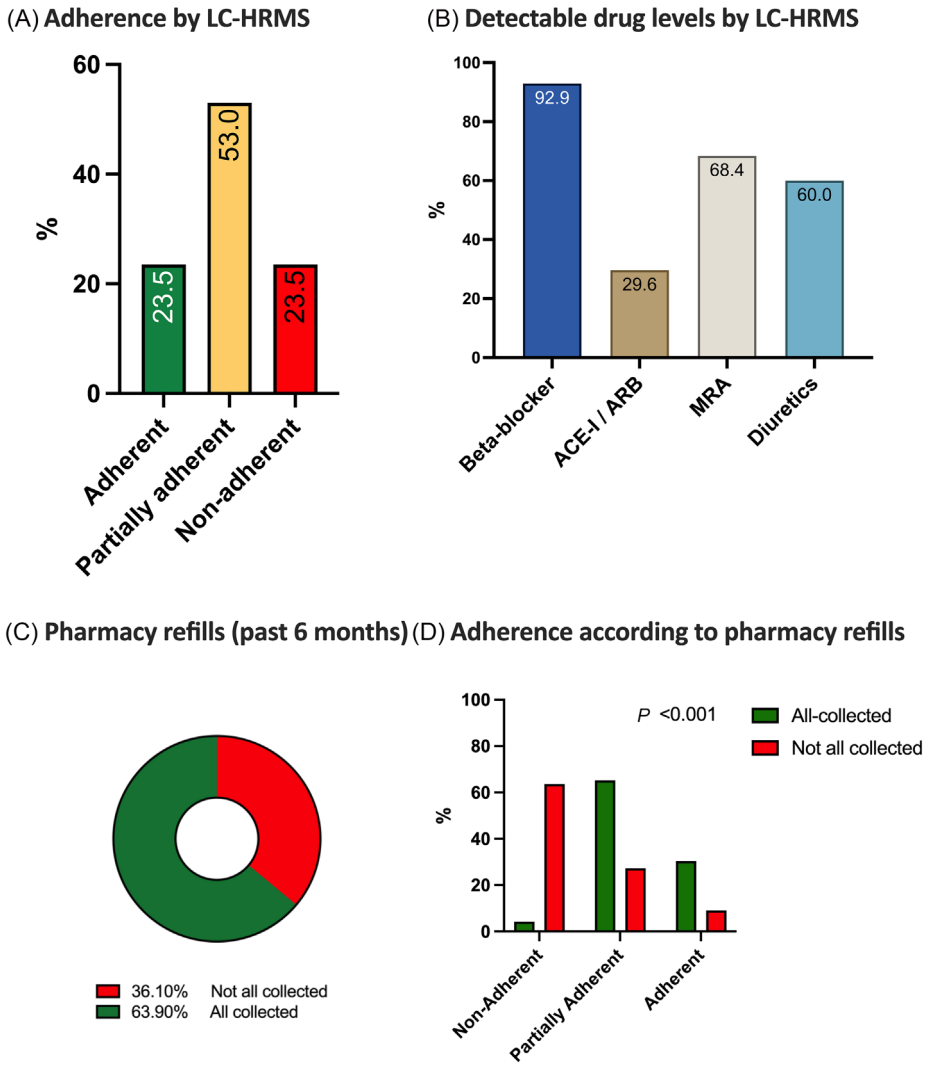


Figure 3 (A) classification to adherent, partially adherent and non-adherent according to LC-HRMS, (B) detectable drug levels by LC-HRMS, (C) pharmacy refills in the past 6 months, (D) association of detectable drug levels and pharmacy refills.

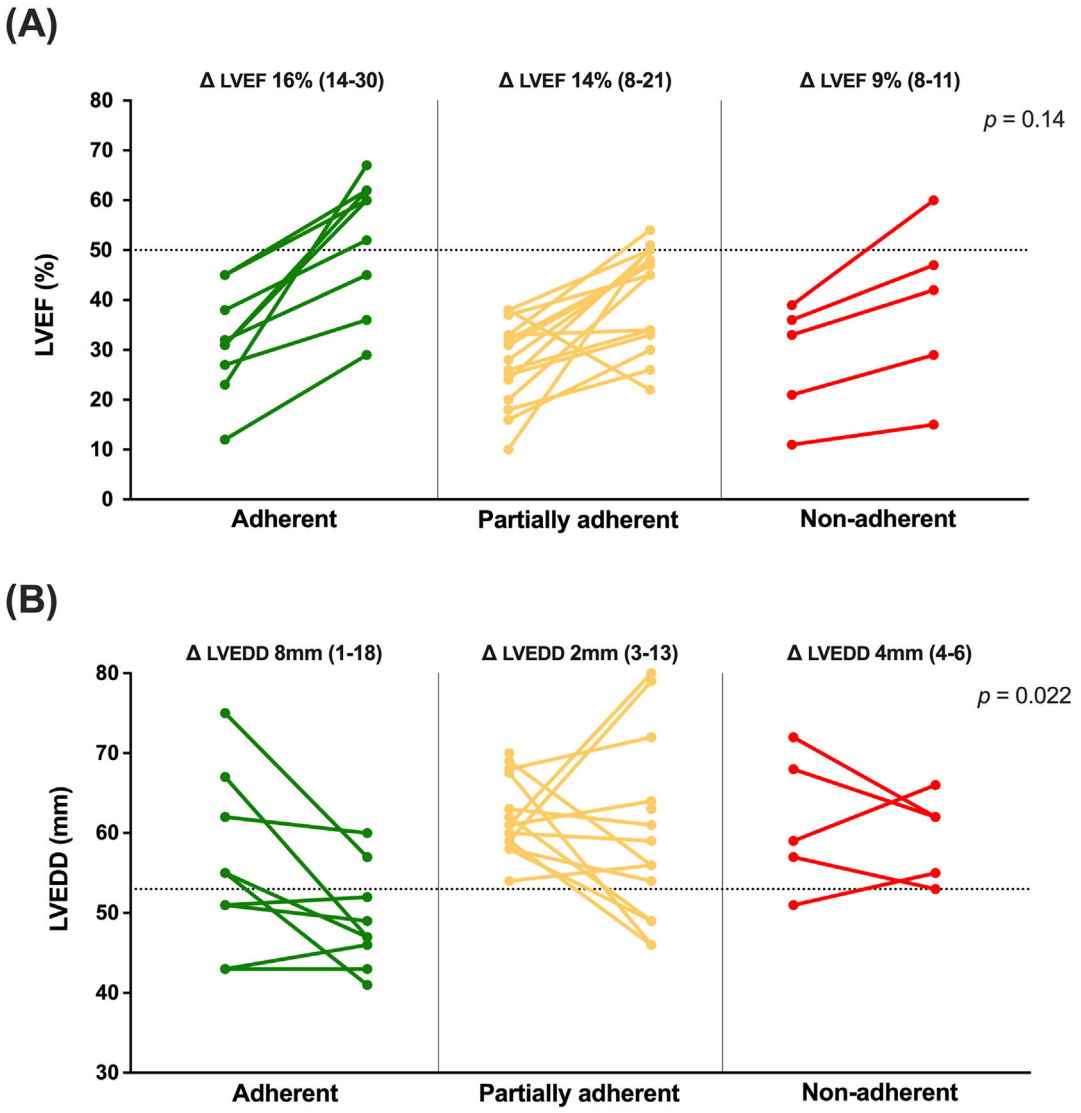


46–52]) than those who were partially or non-adherent (56 mm [IQR 49–63.5], and 62 mm [IQR 55–64], respectively, $P = 0.022$). Although not statistically significant, the LVEF was higher in adherent patients (60% [IQR 41–65]), as compared with those who were partially (46% [IQR 34–50]) or non-adherent (41% [IQR 29–47], $P = 0.14$) (*Figure 4*). Adherence rates (as measured by LC-HRMS) were not different for those who were diagnosed less than or more than 1 year prior the adherence visit (*Table 3*, *Figure S1*).

Adherent patients had a significantly lower overall EQ-5D score (5.5 [IQR 5–7.5], vs. 6 [IQR 5–7] in partially adherent, and 10 [IQR 8–15] non-adherent patients, $P = 0.032$), suggestive of a better self-rated health status. Non-adherent patients reported higher scores for pain and discomfort, in particular, as compared with those who were at least partially adherent ($P = 0.003$) (*Table 3*, *Figure 5*). Although not statistically significant, the adherent cohort reported the best mobility and self-care (*Table S1*).

Importantly, 38.2% and 26.5% of the cohort had an HADS-A/HADS-D score of ≥ 8 points, respectively, which is suggestive of possible underlying depression or anxiety disorders. The HADS-A score tended to be higher in non-adherent patients (10.5 [IQR 5–13] vs. 4.5 [IQR 2–8] in partially adherent, and 6 [IQR 3.5–8.5] in adherent patients, $P = 0.082$). Similarly, non-adherent patients tended to have a HADS-D score of more than 8 points (50%) more often than their partially adherent and adherent counterparts (11.1% and 37.5% respectively, $P = 0.084$). HADS-A and HADS-D scores

Figure 4 Association between adherence and LV reverse remodelling. (A) LVEF (%) and (B) LVEDD (mm).



did not differ between those who collected their medication or not (Table 4).

Discussion

To the best of our knowledge, this is the first study to investigate adherence to HF therapy in patients with PPCM. We found that this South African cohort of patients with PPCM had suboptimal adherence to HF therapy. This could be explained by the lack of support structures (i.e. many patients relied on public transport to collect their medication, few used reminders or had a medication plan of their treatment). Adherence was associated with better LV reverse remodelling, higher self-rated quality of life, and less anxiety and depression.

Adherence is fundamental for successful pharmacological treatment of HF. It is of even greater importance in a setting of a potentially reversible form of heart failure, such as PPCM. In a meta-analysis of 569 studies reporting on adherence to medical treatment, the average rate of non-adherence was reported to be 24.8%.[15] Previous studies on patients with HF showed that non-adherence rates ranged widely depending on the methods used to assess adherence. In a cohort of 341 patients with stable, chronic HF non-adherence rates were 25% using LC-HRMS measurements.[16] In another study on HF patients with a recent admission for HF, 17.6% were classi-

Table 3 Clinical characteristics, functional and mental health scores of patients classified as adherent, partially adherent and non-adherent by means of liquid chromatography high-resolution mass spectrometry (LC-HRMS)

	Total $N = 34$	Non-adherent $N = 8$	Partially adherent $N = 18$	Adherent $N = 8$	*P*-value
NYHA FC at adherence visit					0.15
I	27 (79.4)	5 (62.5)	14 (77.8)	8 (100.0)	
II	2 (5.9)	0 (0.0)	2 (11.1)	0 (0.0)	
III	5 (14.7)	3 (37.5)	2 (11.1)	0 (0.0)	
6-MWT at adherence visit (m)	450.0 (400.0–500.0)	450.0 (400.0–500.0)	462.5 (400.0–500.0)	462.5 (400.0–525.0)	0.92
SBP at adherence visit (mmHg)	121.0 (112.0–136.0)	132.0 (119.0–140.5)	119.0 (112.5–137.5)	112.0 (102.0–123.0)	0.077
DBP at adherence visit (mmHg)	70.0 (60.0–87.0)	85.0 (68.0–90.0)	70.0 (60.0–84.5)	64.0 (52.0–69.0)	0.071
QRS rate at adherence visit (b.p.m.)	72.0 (65.5–83.5)	77.0 (71.0–81.5)	70.0 (65.0–85.0)	69.0 (65.0–84.0)	0.64
LVEDD at adherence visit (mm)	55.0 (49.0–62.0)	62.0 (55.0–64.0)	56.0 (49.0–63.5)	47.0 (46.0–52.0)	0.022
LVESD at adherence visit (mm)	42.0 (34.0–51.0)	51.0 (49.0–57.0)	43.0 (35.0–54.0)	31.0 (28.0–42.0)	0.027
LVEF at adherence visit (%)	46.0 (34.0–54.5)	41.0 (29.0–47.0)	46.0 (34.0–50.0)	60.0 (40.5–64.5)	0.14
Recovered LVEF[a]	12 (37.5)	1 (16.7)	6 (33.3)	5 (62.5)	0.18
Improvement in LVEF	14.5 (8.0–21.0)	9.0 (8.0–11.0)	14.0 (8.0–21.0)	16.0 (14.0–30.0)	0.13
LV reverse remodelling[b]	12 (41.4)	0 (0.0)	6 (37.5)	6 (85.7)	0.007
Improvement in LVEDD	−4.0 (−13.0 to 3.0)	−4.0 (−6.0 to 4.0)	−2.0 (−13.0 to 3.0)	−8.0 (−18.0 to 1.0)	0.42
HADS-A at adherence visit	5.0 (2.0–10.0)	10.5 (5.0–13.0)	4.5 (2.0–8.0)	6.0 (3.5–8.5)	0.082
HADS-A ≥ 8	13 (38.2)	5 (62.5)	5 (27.8)	3 (37.5)	0.24
HADS-D at adherence visit	5.0 (3.0–8.0)	7.5 (5.5–10.0)	3.5 (1.0–7.0)	4.5 (3.5–11.0)	0.12
HADS-D ≥ 8	9 (26.5)	4 (50.0)	2 (11.1)	3 (37.5)	0.084
EQ-5D score	6.0 (5.0–8.0)	10.0 (8.0–15.0)	6.0 (5.0–7.0)	5.5 (5.0–7.5)	0.032
Self-reported adherence	17 (50.0)	4 (50.0)	11 (61.1)	2 (25.0)	0.24

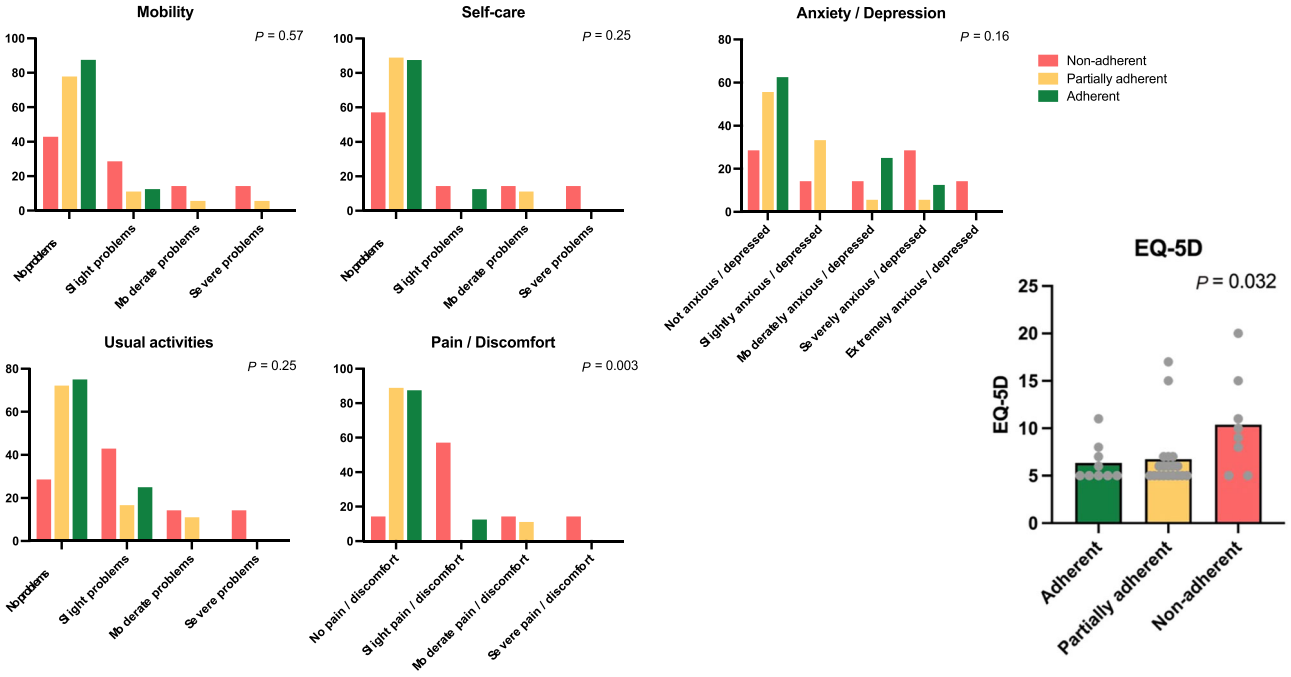
Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.
6-MWT, 6-min walk test; DBP, diastolic blood pressure; EQ 5D, European Quality of Life 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA FC, New York Heart Association functional class; SBP, systolic blood pressure.
[a]'Recovered LVEF' refers to LVEF ≥ 50% at adherence visit.
[b]'LV reverse remodelling' refers to LVEDD ≤ 52 mm at adherence visit.

Table 4 Clinical characteristics, functional and mental health scores of patients who collected all pharmacy refills in the past 6 months, or not

	Total $N = 36$	Not all collected $N = 13$	All collected $N = 23$	*P*-value
NYHA FC at adherence visit				0.072
I	29 (80.6)	8 (61.5)	21 (91.3)	
II	2 (5.6)	1 (7.7)	1 (4.3)	
III	5 (13.9)	4 (30.8)	1 (4.3)	
6-MWT at adherence visit (m)	450.0 (400.0–500.0)	425.0 (400.0–500.0)	475.0 (400.0–525.0)	0.26
SBP at adherence visit (mmHg)	121.0 (115.0–134.0)	122.0 (116.0–136.0)	119.0 (111.0–132.5)	0.57
DBP at adherence visit (mmHg)	70.0 (62.0–87.0)	82.0 (63.0–87.0)	69.5 (61.0–83.5)	0.52
QRS rate at adherence visit (b.p.m.)	73.5 (66.0–85.0)	81.0 (71.0–85.0)	70.0 (65.0–83.0)	0.17
LVEDD at adherence visit (mm)	55.0 (48.0–62.0)	61.0 (46.0–64.0)	53.0 (49.0–59.0)	0.48
LVESD at adherence visit (mm)	42.0 (34.0–51.0)	46.5 (35.0–57.0)	41.0 (34.0–51.0)	0.55
LVEF at adherence visit (%)	47.0 (34.0–55.0)	45.0 (29.0–60.0)	47.0 (34.0–55.0)	0.57
Recovered LVEF	14 (41.2)	4 (36.4)	10 (43.5)	0.69
Improvement in LVEF	14.5 (8.0–21.0)	11.5 (8.0–17.0)	15.0 (10.0–23.0)	0.33
Improvement in LVEDD	−2.0 (−13.0 to 3.0)	−2.0 (−10.0 to 4.0)	−3.0 (−13.0 to 2.0)	0.59
LV reverse remodelling	13 (41.9)	3 (30.0)	10 (47.6)	0.35
HADS-A at adherence visit	5.0 (2.0–9.5)	6.0 (5.0–11.0)	4.0 (2.0–8.0)	0.088
HADS-A ≥ 8	13 (36.1)	6 (46.2)	7 (30.4)	0.35
HADS-D at adherence visit	4.5 (2.5–7.5)	6.0 (4.0–8.0)	4.0 (1.0–7.0)	0.22
HADS-D ≥ 8	9 (25.0)	4 (30.8)	5 (21.7)	0.55
EQ-5D score	6.0 (5.0–8.0)	7.0 (5.0–10.5)	6.0 (5.0–7.0)	0.38
Self-reported adherence	18 (50.0)	6 (46.2)	12 (52.2)	0.73
Adherence by drug levels				<0.001
Non-adherent	8 (23.5)	7 (63.6)	1 (4.3)	
Partially adherent	18 (52.9)	3 (27.3)	15 (65.2)	
Adherent	8 (23.5)	1 (9.1)	7 (30.4)	

Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.
6-MWT, 6-min walk test; DBP, diastolic blood pressure; EQ-5D, European Quality of Life 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA FC, New York Heart Association functional class; SBP, systolic blood pressure.

Figure 5 Components of the EQ-5D-5L (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) according to adherence category.



fied as partially or completely non-adherent using liquid chromatography–tandem mass spectrometry of urine samples.[17] In our study, 23.5% of PPCM patients were classified as non-adherent. However, in the context of the differing methods used for the assessment of adherence rates, drawing direct comparisons remains difficult.

Adherence to complex HF treatment has previously been shown to be a substantial problem in South Africa.[18] Various factors contribute to non-adherence. Side effects of medication are frequently recognized to play a part in non-adherence.[19] Complexity of treatment,[20] patients' lack of belief in the benefit of the treatment and/or their lack of insight into the illness were also highlighted as reasons to discontinue medication.[21] Moreover, inadequate follow-up or discharge planning further contributes to non-adherence.[22] It has to be highlighted that the majority of patients in this cohort came from a low socio-economic background, and often relied on public transport to travel to health care facilities where they could collect thir medication. The complexity of HF treatment, as well as the low utilization of drug reminders such as a medication plan, pill boxes or similar reminders may have contributed to the high rates of partial adherence and non-adherence among participants in this study. Sewitch *et al.*[22] described treatment of asymptomatic disease as a risk factor for non-adherence. This risk factor may play an important role in the setting of PPCM. Approximately 80% of the cohort were asymptomatic (i.e. NYHA FC I) at the time of the adherence visit, and they might not have appreciated the seriousness of the disease and/or understood the importance of adherence to their medication. About one third of patients admitted in the interview to have interrupted their treatment, as they did not think it was necessary to take their medication anymore. In some forms of dilated cardiomyopathy (DCM), withdrawal of drug therapy resulted in relapse of LV dysfunction and HF.[23] The safety of discontinuing drug therapy in patients with recovered LVEF has not been prospectively studied in PPCM, as yet.

Depression and anxiety are well-known risk factors for poor adherence to medication.[19,20,24] A recent study from Germany showed a significantly higher prevalence of mental disorders such as major depressive disorders (MDD), post-traumatic stress disorder (PTSD), and panic disorder in PPCM compared with postpartum controls. It was shown that patients with PPCM had an impaired tryptophan metabolism with elevated levels of serum kynurenine and reduced levels of serum serotonin as well as elevated levels of the depression-associated miR-30e.[25] This suggests that patients with PPCM might have a potential predisposition for mental disorders, at the time of diagnosis. Albeit not statistically significant in our study, the HADS-A/D scores tended to be higher in non-adherent patients. Moreover, about a quarter of patients had an HADS-D of at least 8, indicating a possible underlying depressive disorder. In addition, almost 40% of the cohort had an HADS-A of at least 8 points suggestive of an underlying anxiety disorder.

In our study, adherent patients scored significantly better for their self-rated health-status as assessed by the EQ-5D score. Lower health-related quality of life as assessed by EQ-5D score and symptoms of depression as assessed by HADS-D score have previously been shown to be associated with a higher subsequent risk of non-adherence in patients with HF.[26] In this regard, it could mean that patients who are limited by their mobility, pain or discomfort are less likely to collect their medication from the pharmacy and are thus categorized as non-adherent. However, it needs to be pointed out that adherence rates and mental health status are mere associations and no conclusion regarding causality can be made between these.

Limitations

Considering that PPCM is a relatively rare disease, we acknowledge that the sample size of this single centre study is small and affected the precision of estimates. However, a post hoc power calculation was performed comparing our study's adherence rates (22.2% having all drugs detected in their blood), compared with the study by Pelouch et al.,[16] who also used LC-HRMS to detect drug levels and found 75% of patients with stable chronic HF were fully adherent. Considering an alpha of 0.05, our study was adequately powered with a cohort of only 36 patients.[27]

The LC-HRMS measurements used in this study provide an objective measurement of adherence to all prescribed HF drugs in the day(s) before the outpatient visit. However, this method provides a mere 'snapshot', rather than a longitudinal testing of adherence. We acknowledge, that an upcoming clinic visit could have influenced the short-term adherence to medication, although participants were not aware that their adherence to medication would be assessed on that day. Future studies should focus on longitudinal testing of adherence in women with PPCM.

Given pharmacokinetics of enalapril with its relatively short half-life ($T_{1/2}$) of approximately 0.5–6.1 h, the adherence to enalapril in this study may have been underestimated. However, we believed that using this conservative approach reduces the risk of miss-classifying patients as adherent.

Conclusions

In this prospective, single-centre study we found that adherence to HF therapy was associated with better LV reverse remodelling in patients with PPCM. Higher rates of adherence were associated with better self-rated health status. Using objective measures of adherence in clinical practice may help to identify non-adherent patients who could be referred for intensified education and counselling about the importance of drug therapy for LV recovery in PPCM. Screening of pharmacy refills in the months prior to the clinic visit may be used as a cost-effective screening strategy to detect non-adherent patients. It also provides important insights into the barriers to adherence that women with PPCM face and show that anxiety and depression may be a frequent underlying co-morbidity in this condition. Our study highlights the importance of regular follow-up appointments to monitor adherence and adjust HF treatment as necessary.

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Conflict of interest

The authors report no conflicts of interest related to this manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Self-rated health-status according to EQ5D in non-adherent, partially adherent and adherent participants.
Figure S1: Adherence as measured by LC-HRMS among patients who were followed-up within one year or more than one year after diagnosis.

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