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RESEARCH ARTICL

Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF)

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Aims

Heart failure (HF) leads to repeat hospitalisations and reduces the duration and quality of life. Pulmonary artery pressure (PAP)-guided HF management using the CardioMEMS™ HF system was shown to be safe and reduce HF hospitalisation (HFH) rates in New York Heart Association (NYHA) class III patients. However, these findings have not been replicated in health systems outside the United States. Therefore, the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF) evaluated the safety, feasibility, and performance of this device in Germany, The Netherlands, and Ireland.

Methods and results

A total of 234 NYHA class III patients (68 ± 11 years, 22% female, ≥1 HFH in the preceding year) from 31 centres were implanted with a CardioMEMS sensor and underwent PAP-guided HF management. One-year rates of freedom from device- or system-related complications and from sensor failure (co-primary outcomes) were 98.3% [95% confidence interval (CI) 95.8–100.0] and 99.6% (95% CI 97.6–100.0), respectively. Survival rate was 86.2%. For the 12 months post- vs. pre-implant, HFHs decreased by 62% (0.60 vs. 1.55 events/patient-year; hazard ratio 0.38, 95% CI 0.31–0.48; $P < 0.0001$). After 12 months, mean PAP decreased by 5.1 ± 7.4 mmHg, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall/clinical summary scores increased from 47.0 ± 24.0/51.2 ± 24.8 to 60.5 ± 24.3/62.4 ± 24.1 ($P < 0.0001$), and the 9-item Patient Health Questionnaire sum score improved from 8.7 ± 5.9 to 6.3 ± 5.1 ($P < 0.0001$).

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Conclusion Haemodynamic-guided HF management proved feasible and safe in the health systems of Germany, The Netherlands, and Ireland. Physician-directed treatment modifications based on remotely obtained PAP values were associated with fewer HFH, sustainable PAP decreases, marked KCCQ improvements, and remission of depressive symptoms.

Keywords Heart failure • Morbidity • Haemodynamic monitoring • CardioMEMS™ HF system • Health-related quality of life • Depression

Introduction

Heart failure (HF) affects over 64 million people worldwide, accounts for >1 million hospital admissions annually in the United States (US) and Europe, and is associated with high societal and economic costs.[1,2] Soon after discharge, many HF patients experience symptom recurrence, requiring early readmission.[3] Each HF-related hospitalisation (HFH) increases the risk for subsequent events.[4] Healthcare providers and payers therefore place increasing importance on outpatient HF management strategies.

Heart failure is associated with significant functional limitations and impaired quality of life (QoL)[5]; studies suggest that those with severe symptoms would consider trading longer life for better quality.[6] In addition to traditional endpoints, the importance of patient-reported outcomes (PROs) in HF is increasingly recognised,[7] and PROs reflecting the burden of disease are recommended as endpoints for evaluating treatment efficacy.[8] Health status (symptoms, physical function, QoL) independently predicts mortality risk,[9,10] and close interrelation between health status and patient-reported depressive symptoms has been proposed to explain the adverse prognostic significance of depression in HF patients.[9]

The risk for adverse clinical outcomes increases when pulmonary artery pressure (PAP) rises, typically days or weeks before clinical HF signs and symptoms develop.[11] Lowering PAP is associated with improved clinical outcomes.[11,12] In the US, the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Functional Class III Heart Failure Patients (CHAMPION) trial demonstrated that haemodynamic-guided pharmacotherapy reduced HFH risk in outpatients with advanced HF, irrespective of left ventricular ejection fraction (LVEF).[13–16] However, differences in HF care between health systems might critically impact clinical outcomes. Furthermore, information on the effects of haemodynamic-guided HF management on PROs is lacking. Therefore, the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF) evaluated the safety, feasibility, and performance of this strategy using the CardioMEMS™ HF system in several European health systems.[17]

Methods

Study design and participants

MEMS-HF is a prospective non-randomised multicentre study (NCT02693691) designed to characterise the utility of the CardioMEMS™ HF system (Abbott, Sylmar, CA, USA) over 12-month follow-up in Germany (26 centres), The Netherlands (4 centres) and Ireland (1 centre) (see online supplementary *Appendix S1* for details). The study protocol was approved by all responsible ethics committees. Study design information has been reported previously.[17] All participants provided written informed consent and were followed until the last patient completed 12-month follow-up. MEMS-HF was conducted according to Good Clinical Practice guidelines and 2002 Declaration of Helsinki principles.

Males and females aged ≥18 years with predominant New York Heart Association (NYHA) class III symptoms over the last month and ≥1 HFH in the previous year were eligible. Patients with reduced LVEF needed to be on guideline-directed medical therapies (GDMT) as tolerated.[18] Candidates for heart transplant, ventricular assist device implantation or hospice care were excluded (online supplementary *Table S1*).

Procedures

Study physicians underwent formal implant training. Non-physician caregivers were offered education in HF disease management strategies[19] and received written instructions about how to apply PAP-guided care.[17] Study data were collected at baseline, during implant, before discharge, after 6 and 12 months, and every 6 months until the last patient completed 12-month follow-up. At study visits, documentation of HFH events, NYHA class assessment and physical examination were performed as applicable. Changes in HF medications or other treatments, reasons for changes, and any incident (serious) device-related or other adverse events (AEs) were recorded.

Qualifying patients underwent right heart catheterisation with limited pulmonary angiography to identify a pulmonary artery branch suitable for sensor insertion. The sensor was calibrated after deployment. A 30-day safety follow-up was scheduled if sensor implantation was attempted, but unsuccessful.

Before discharge, each patient received a Patient Electronics Unit to upload resting, supine PAP information from the sensor to a secure website (*Merlin.net*™, Abbott, Sylmar, CA, USA). Local study teams trained patients in device usage, ensured that they understood their responsibility for daily PAP measurement, and provided information and materials enabling self-monitoring of vital parameters and HF signs/symptoms as used in the Interdisciplinary Network for Heart Failure (INH) study.[19]

Uploaded PAP information was reviewed at least weekly by local study personnel. Additional PAP reviews were triggered by email notifications of PAP excursions outside the user-defined thresholds automatically issued by the *Merlin.net*™ system. Investigators responded to PAP deviations according to pre-defined algorithms[17] and were requested to document the timing, type, and reasons for HF medication changes. Treatment adjustments were communicated directly to patients. Subsequently, PAP trends were monitored at shorter intervals until resolution of the PAP deviation, which was again communicated to patients. Irrespective of PAP trends, patients were contacted weekly by

their caregiver for the first month post-implant and every 2–4 weeks thereafter. During these telephone calls, coaching was applied regarding self-care, effects of HF medications, and treatment adherence; dose adjustments of neurohormonal inhibitors were pursued, as tolerated.[19]

Patient-reported outcomes were assessed at baseline, 6, and 12 months. The Kansas City Cardiomyopathy Questionnaire (KCCQ)[20] was used to capture health status (possible score 0–100; higher scores indicate better health status). Depressive symptoms were assessed using the 9-item Patient Health Questionnaire depression module (PHQ-9)[21] [score 0–3 per item (sum-score 0–27); higher values indicate more severe depression]. Additionally, patients completed the EQ-5D-5L questionnaire including a visual analogue scale (EQ-VAS), where respondents rate their current overall generic health on a 0–100 hash-marked VAS.[22]

Endpoints

Co-primary safety endpoints were device- or system-related complications (DSRC), defined as a (serious) AE definitely or possibly related to the PAP sensor or external electronics that was treated invasively or resulted in patient death or explant of the device. Pressure sensor failure was defined as an inability to obtain readings after troubleshooting the system to exclude problems with external electronics.

Additional endpoints included: annualised HFH rate during 12 months after vs. 12 months before implant (secondary endpoint); 12-month all-cause death rate; PAP change from baseline; changes in the KCCQ clinical and overall summary scores (CSS, OSS),[20] PHQ-9 sum score,[21] and EQ-VAS score[22] at 6 and 12 months; changes in HF medications and NYHA class at 6 and 12 months; patient compliance with taking PAP readings, and healthcare provider compliance for weekly PAP readings. Changes in natriuretic peptide (NP) levels were assessed in patients who had serial measurements available.

Data analysis and statistics

The study had two co-primary safety endpoints: freedom from DSRC >80%; and freedom from pressure sensor failure >90% at 12 months, which were evaluated using an exact test for one-sample binomial proportions. Performance was assessed by comparing the annualised 12-month HFH rate post- vs. pre-implant using the Anderson–Gill extension of the Cox proportional hazards model. Twelve-month all-cause mortality was reported using the Kaplan–Meier method.

Cumulative changes from baseline in diastolic, systolic and mean PAP (dPAP, sPAP, mPAP) were evaluated using an area-under-the-curve (AUC) analysis, which quantifies frequency and duration of PAP values below baseline (first week of home readings) using numeric integration. AUCs were analysed for all patients who had post-implant PAP readings from the first week available as reference ($n = 227$), and for subgroups according to baseline mPAP (<35 and ≥35 mmHg). In addition, crude baseline, 6- and 12-month PAP values and their changes were computed for each time-point. Changes in AUC and PAP were analysed using paired *t*-tests. Compliance with daily PAP readings was calculated as total number of readings divided by number of days a patient was under study. Weekly compliance was calculated for each patient and used to derive mean weekly compliance for the entire population. Changes in NYHA class at 6 and 12 months were analysed using a Wilcoxon signed rank test. Mean changes in NP levels and in KCCQ, PHQ-9 and EQ-VAS scores at 6 and 12 months were analysed using least-squares means.

Descriptive statistics are presented as number of observations, mean and standard deviation, or median/interquartile range (as applicable) for continuous variables, and as counts and percentages/rates for categorical variables. Safety analyses included all patients providing written informed consent and receiving a sensor implant or undergoing the implant procedure but not receiving a sensor. Efficacy analyses included all patients receiving a sensor implant.

Two-sided *P*-values <0.05 were considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

Results

Patients

Between 13 May 2016 and 29 March 2018, 239 patients were enrolled (see online supplementary *Table S2* for recruitment by site); 236 entered the safety analysis and 234 the efficacy analysis; no patient was lost to follow-up (*Figure 1*). Patients were elderly, mostly male, had many comorbidities and were receiving optimal drug- and device-based HF therapy; most had undergone HFH within the past 3 months (*Table 1*). Baseline PRO assessments indicated impaired health status and low mood.

Safety endpoints

After 1 year, 235/239 patients [98.3%, 95% confidence interval (CI) 95.8–100.0%] were free from DSRC and 233/234 (99.6%, 95% CI 97.6–100.0%) were free from pressure sensor failure (*Figure 2A,B*). There were 21 serious AEs during 236 implant attempts, of which 4 were categorised as DSRC and 21 as procedure-related. No DSRC required sensor removal. In one case, a sensor was implanted, but readings were not obtainable. Most (serious) adverse device-related events were procedure-related (online supplementary *Tables S3 and S4*).

Clinical outcomes

At 12-month follow-up, 91 patients (38.9%) had experienced ≥1 HFH; in most patients (27.8%) events occurred during the first 6 months post-implant. Compared with the pre-implant year, the HFH rate decreased by 62% [0.60 vs. 1.55 events/patient-year; hazard ratio (HR) 0.38, 95% CI 0.31–0.48; $P < 0.0001$; *Figure 2C*]; the corresponding reduction in patients completing ≥12-month follow-up was 66% (HR 0.34, 95% CI 0.26–0.44; $P < 0.0001$). Reductions in the HFH rate were consistent irrespective of sex, age, HF aetiology, device use, LVEF, baseline mPAP and important comorbidities (*Figure 3*). After 6 and 12 months, 16 and 31 patients (7.0% and 13.8%), respectively, had died (online supplementary *Table S5*); no deaths were considered related to the device, delivery system, or a protocol-required procedure. All 'unknown' deaths occurred outside the 30-day implant procedure safety window.

Pulmonary artery pressure decreased progressively over time. Average changes in dPAP, sPAP, and mPAP, respectively, were -3.1 ± 5.1, -3.4 ± 7.7 and -3.3 ± 6.1 mmHg at 6 months, and -4.6 ± 6.2, -5.5 ± 9.3, and -5.0 ± 7.3 mmHg at 12 months (all $P < 0.0001$ vs. baseline); similar reductions were seen in PAP

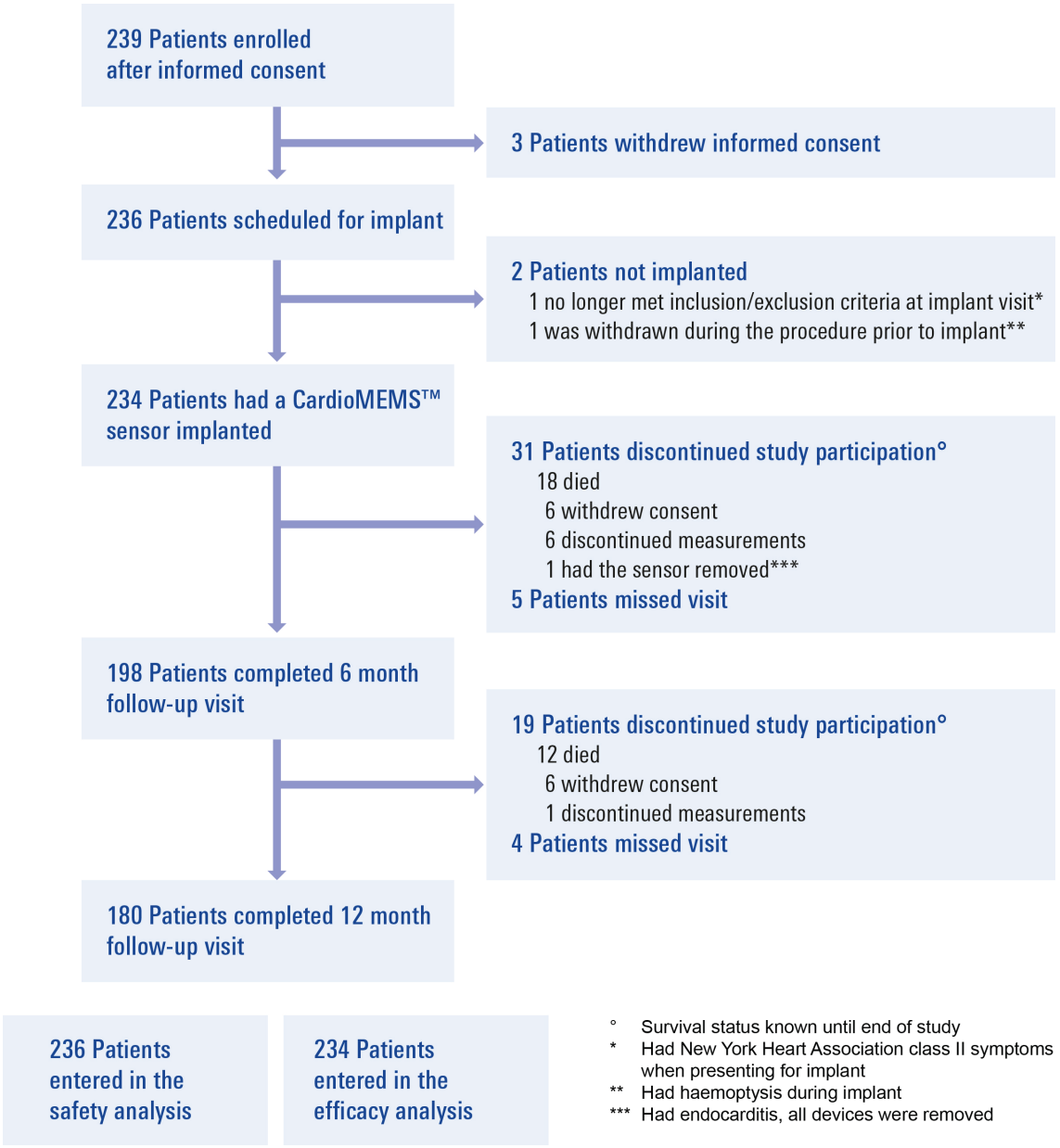


Figure 1 Study flow and patient disposition.

AUC (online supplementary *Table S6*). Both absolute and AUC PAP decreases were significantly greater in patients with baseline mPAP ≥35 vs. <35 mmHg. Across the entire sample, regression of 12-month changes in mean PAP (AUC) against baseline mPAP had a slope of −125 mmHg-days (online supplementary *Figure S1*).

The NYHA class improved in 89 patients (38%) at 6 months and 83 patients (35.5%) at 12 months; at both times, four patients (1.7%) had worsened to NYHA class IV (online supplementary *Figure S2*). In 130 patients with NP assessments before and at least once after implant, levels decreased by ≥20% in 71 (54.6%) and by ≥30% in 61 (46.9%). In 82 patients with three consecutive measurements, amino-terminal pro-B-type NP levels decreased progressively from 4561 ± 7331 pg/mL at baseline to 3064 ± 4421 pg/mL at 6 months ($P = 0.003$) and 2943 ± 3503 pg/mL at 12 months ($P = 0.027$) (online supplementary *Figure S3*).

Patient and caregiver adherence

Mean [median (interquartile range)] patient adherence to daily PAP transmissions was 78.1 ± 23.5% [87.6% (69.4–94.9%)]. Weekly compliance was 89.7 ± 17.8% [97.2% (88.6–100.0%)]. Caregiver adherence to weekly review of PAP data was 89.8 ± 18.7% [100% (87.4–92.2%)].

Table 1 Baseline characteristics

Characteristic	Efficacy population ($n = 234$)
Age (years)	67.9 ± 10.7
Female sex	51 (21.8)
Heart rate (bpm)	71.2 ± 12.0
Systolic blood pressure (mmHg)	116.5 ± 16.8
Diastolic blood pressure (mmHg)	68.8 ± 11.1
Body mass index (kg/m^2)	28.8 ± 5.3
Disease history/risk factors	
Atrial arrhythmia	144 (61.5)
Ventricular arrhythmia	53 (22.6)
Diabetes mellitus	107 (45.7)
Chronic kidney disease	135 (57.7)
Cerebrovascular insult	30 (12.8)
Chronic obstructive pulmonary disease	48 (20.5)
Hyperlipidaemia	140 (59.8)
Myocardial infarction	95 (40.6)
Heart failure characteristics	
Ischaemic cardiomyopathy	125 (53.4)
Hospitalised for heart failure within 6 (3) months before implant	89.1 (75.1)
New York Heart Association class III	234 (100)
NT-proBNP, median (interquartile range)[a] (pg/mL)	2379 (1270, 4989)
LVEF (%)	33.0 ± 15.1
LVEF <40%	167 (72.3)
LVEF ≥40%	64 (27.7)
Heart failure therapy	
ACEi/ARB/ARNi	200 (85.5)
Beta-blocker	208 (88.9)
MR antagonist	169 (72.2)
Diuretic	225 (96.2)
Implantable cardioverter-defibrillator	91 (38.9)
Cardiac resynchronisation therapy	63 (26.9)
Baseline haemodynamics[b]	
Systolic PAP (mmHg)	47.0 ± 16.9
Diastolic PAP (mmHg)	19.4 ± 8.1
Mean PAP (mmHg)	30.3 ± 10.7
Pulmonary arterial wedge pressure (mmHg)	19.7 ± 9.4
Transpulmonary pressure gradient (mmHg)	10.6 ± 7.1
Cardiac index (L/min/m^2)	2.0 ± 0.6
Pulmonary vascular resistance (Wood units)	2.8 ± 2.2
Patient-reported outcomes	
Kansas City Cardiomyopathy Questionnaire	
Overall summary score	47.0 ± 24.0
Clinical summary score	51.2 ± 24.8
9-Item Patient Health Questionnaire (sum score)	8.7 ± 5.9
EQ-5D-5L visual analogue scale	54.4 ± 20.7

Values are mean ± standard deviation, or *n* (%), unless stated otherwise.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PAP, pulmonary artery pressure.
[a] $n = 178$.
[b] Data obtained during baseline right heart catheterisation.

Patient-reported outcomes

All PRO metrics improved substantially after 6 months, and improvements were sustained at 12 months (*Table 2*). At 6 or 12 months, improvements of ≥10 in the KCCQ CSS were observed in 101 patients (52%) and in the KCCQ OSS in 109 patients (56%). Patients with vs. without a ≥10-point increase in CSS had significantly greater mPAP decreases at 6 and 12 months [−4.6 ± 6.8 vs. −2.6 ± 5.6 mmHg ($P = 0.026$, $n = 187$) and −6.7 ± 8.1 vs. −3.7 ± 6.6 mmHg ($P = 0.010$, $n = 167$)]. Corresponding dPAP decreases at 6 and 12 months were −4.3 ± 5.8 vs. −2.4 ± 4.5 mmHg ($P = 0.017$, $n = 187$) and −6.2 ± 7.0 vs. −3.2 ± 5.2 mmHg ($P = 0.002$, $n = 167$). KCCQ OSS results were comparable. Concordantly, greater improvements in the PHQ-9 sum score and the EQ-VAS score were observed in patients with greater PAP decreases. Thus, PROs showed consistently greater improvements in patients with baseline mPAP ≥35 vs. <35 mmHg (*Figure 4*).

Heart failure medication changes

Diuretics were adjusted most often (*Figure 5*). For all substance classes, cumulative medication changes and average rates of monthly changes at a per-patient level were highest during the first 3 months post-implant but continued throughout follow-up.

Discussion

MEMS-HF provides the first European experience with PAP-guided HF therapy. The study demonstrated that this is a safe and feasible strategy to remotely manage outpatients in Germany, The Netherlands and Ireland. The primary safety objective was achieved, since 98.3% patients remained free from DSRC. Implant procedure safety and DSRC rates compared favourably to those reported for permanent therapeutic implants used in HF management,[13] were similar to those of right heart catheterisation,[23] and none were fatal or required sensor removal. Feasibility was tested in high-risk patients with NYHA class III symptoms despite maximally tolerated GDMT who had been hospitalised at least once during the previous 12 months.

Consistent with previous studies evaluating haemodynamic-guided HF management, including the controlled CHAMPION trial,[11–16] post-implant HFH rates were reduced in MEMS-HF. The uncontrolled study design and potential underestimation of pre-enrolment HFH events due to information bias limit possible inferences. However, consistent results across studies support a role for remote PAP monitoring in guiding HF medication changes and volume management in outpatients. This is particularly relevant for patients with HF and preserved LVEF (HFpEF), for whom no evidence-based therapies are available to date. In the CHAMPION trial, haemodynamic-guided management reduced HFH rates in patients with HFpEF.[15,16] Currently, PAP-guided management represents the only evidence-based strategy for maintaining stability in HFpEF populations.

The rationale for targeting PAP to improve HF outcomes emerged from observations that persistently high values were

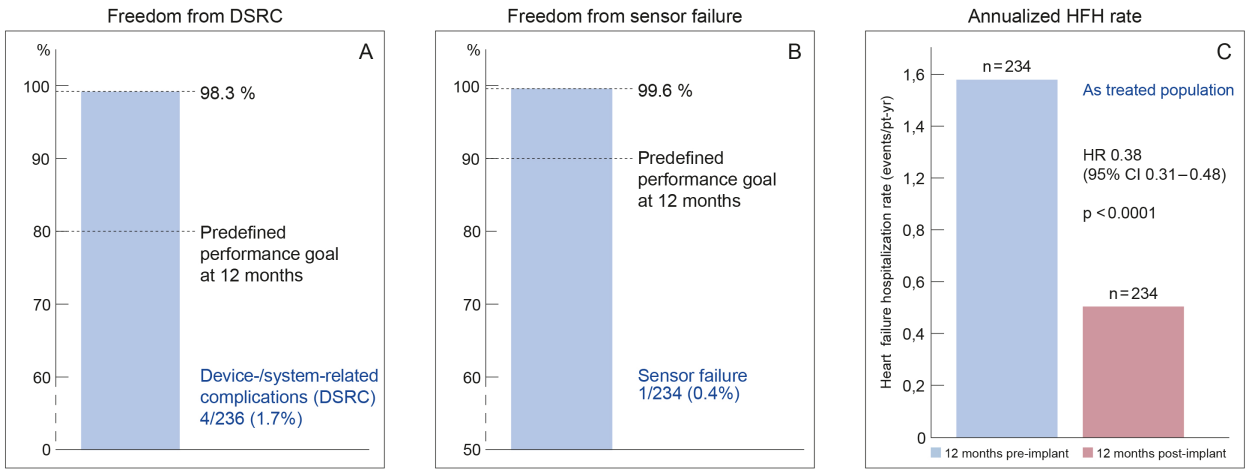


Figure 2 Freedom from co-primary endpoint events and annualised heart failure hospitalisation (HFH) rates in MEMS-HF participants. (*A*) Freedom from device- or system-related complications (DSRC) at 12 months. (*B*) Freedom from sensor failure at 12 months. (*C*) Annualised HFH rate (all patients). CI, confidence interval; HR, hazard ratio.

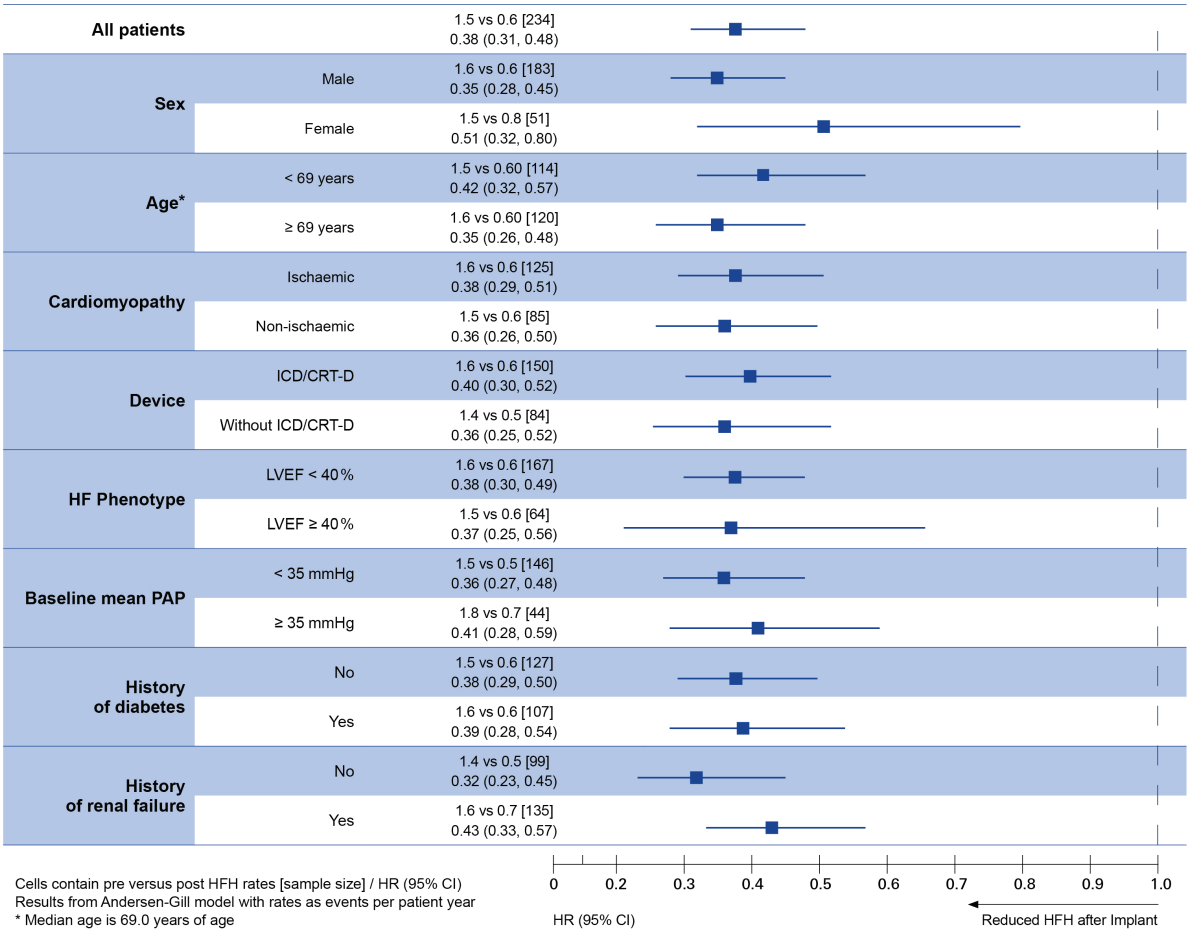


Figure 3 Risk of hospitalisation for heart failure (HFH) in the 12 months post- vs. pre-implant, overall and in pre-specified subgroups. CI, confidence interval; CRT-D, cardiac resynchronisation therapy + defibrillator; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure.

Table 2 Patient-reported outcomes

Questionnaire	Baseline[a]	6 months[a]	Score change and *P*-value (6 months vs. baseline)[b]	12 months	Score change and *P*-value (12 months vs. baseline)[b]
Kansas City Cardiomyopathy Questionnaire					
OSS	47.0 ± 24.0 (227) [43.8, 50.1]	59.8 ± 23.9 (195) [56.4, 63.2]	11.9 ± 1.5 [9.0, 14.9] <0.0001	60.5 ± 24.3 (175) [56.9, 64.1]	12.7 ± 1.6 [9.6, 15.7] <0.0001
OSS mPAP <35 mmHg	51.3 ± 25.3 (103) [46.4, 56.3]	63.0 ± 22.7 (90) [58.2, 67.7]	10.1 ± 1.9 [6.4, 13.8] <0.0001	65.0 ± 22.1 (83) [60.2, 69.8]	12.32 ± 1.9 [8.5, 16.1] <0.0001
OSS mPAP ≥35 mmHg	43.8 ± 22.5 (117) [39.7, 48.0]	57.9 ± 24.8 (100) [53.0, 62.8]	13.9 ± 2.4 [9.2, 18.5] <0.0001	57.0 ± 25.4 (89) [51.6, 62.3]	13.0 ± 2.5 [8.1, 17.8] <0.0001
CSS	51.2 ± 24.8 (227) [48.0, 54.5]	62.0 ± 25.0 (195) [58.4, 65.5]	9.8 ± 1.6 [6.7, 12.9] <0.0001	62.4 ± 24.1 (175) [58.8, 66.0]	10.1 ± 1.6 [6.9, 13.4] <0.0001
CSS mPAP <35 mmHg	57.1 ± 26.4 (103) [51.9, 62.3]	65.3 ± 23.0 (90) [60.5, 70.2]	6.8 ± 2.0 [2.9, 10.6] 0.0007	66.1 ± 22.2 (83) [61.3, 71.0]	7.7 ± 2.0 [3.8, 11.7] 0.0002
CSS mPAP ≥35 mmHg	46.9 ± 22.4 (117) [42.8, 51.0]	60.0 ± 26.5 (100) [54.7, 65.3]	12.8 ± 2.5 [7.9, 17.6] <0.0001	59.6 ± 25.4 (89) [54.2, 64.9]	12.3 ± 2.6 [7.2, 17.4] <0.0001
9-Item Patient Health Questionnaire					
Sum score	8.7 ± 5.9 (225) [7.9, 9.5]	6.7 ± 5.4 (195) [5.9, 7.5]	−1.8 ± 0.3 [−2.4, −1.1] <0.0001	6.3 ± 5.1 (175) [5.6, 7.1]	−2.1 ± 0.4 [−2.8, −1.4] <0.0001
Sum score mPAP <35 mmHg	8.3 ± 6.0 (101) [7.1, 9.5]	6.4 ± 5.6 (90) [5.3, 7.6]	−1.7 ± 0.5 [−2.7, −0.7] 0.0006	6.0 ± 4.9 (83) [4.9, 7.1]	−2.0 ± 0.5 [−3.0, −1.1] <0.0001
Sum score mPAP ≥35 mmHg	8.8 ± 5.8 (117) [7.8, 9.9]	6.8 ± 5.1 (100) [5.8, 7.8]	−1.8 ± 0.5 [−2.8, −0.9] 0.0002	6.4 ± 4.9 (89) [5.3, 7.4]	−2.2 ± 0.5 [−3.2, −1.2] <0.0001
EQ-5D-5L VAS					
VAS	54.4 ± 20.7 (227) [51.7, 57.1]	59.8 ± 21.3 (195) [56.8, 62.8]	4.9 ± 1.5 [1.9, 7.9] 0.0015	61.1 ± 21.1 (174) [58.0, 64.3]	6.1 ± 1.6 [3.0, 9.3] 0.0002
VAS mPAP <35 mmHg	57.5 ± 21.3 (103) [53.3, 61.6]	64.1 ± 20.3 (90) [59.8, 68.3]	6.0 ± 2.2 [1.7, 10.3] 0.0066	63.1 ± 19.2 (83) [58.9, 67.3]	5.1 ± 2.2 [0.7, 9.5] 0.0227
VAS mPAP ≥35 mmHg	51.8 ± 20.4 (117) [48.0, 55.5]	56.4 ± 21.8 (100) [52.0, 60.7]	4.3 ± 2.3 [−0.2, 8.8] 0.0584	59.7 ± 22.8 (88) [54.9, 64.6]	7.4 ± 2.4 [2.7, 12.0] 0.0021

[a]Mean ± standard deviation (*n*) [95% confidence interval].
[b]Least-squares mean difference ± standard error [95% confidence interval].
CSS, clinical summary score; mPAP, mean pulmonary artery pressure; OSS, overall summary score; VAS, visual analogue scale.

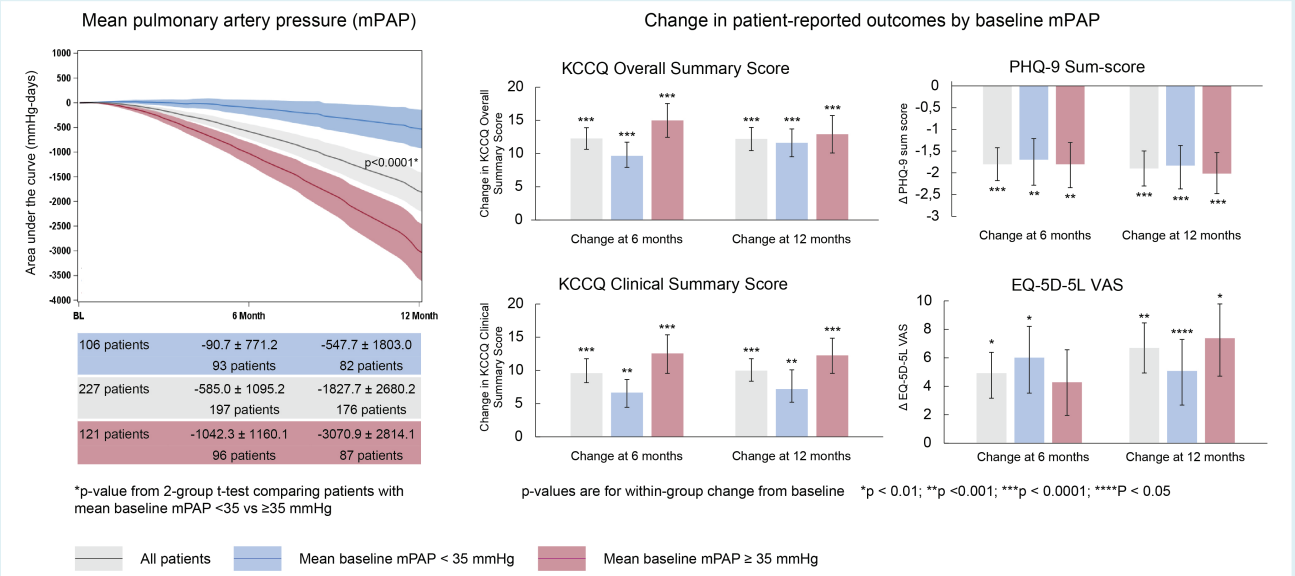
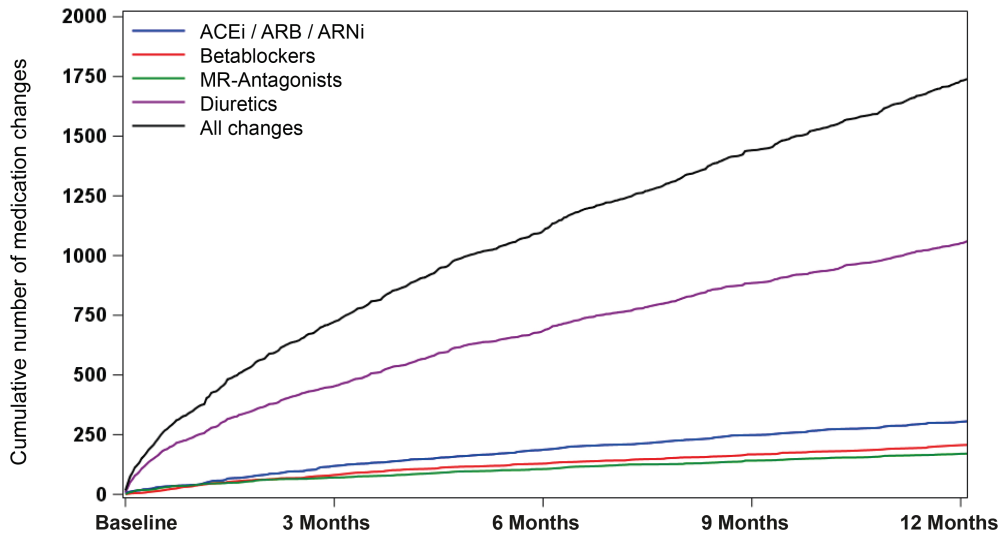


Figure 4 (*Left*) Changes in mean pulmonary artery pressure (mPAP) area under the curve overall (grey) and in subgroups with mPAP <35 mmHg or ≥35 mmHg. (*Right*) Changes in patient-reported outcomes at 6- and 12-month follow-up by baseline mPAP. CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; PHQ-9, 9-item Patient Health Questionnaire; VAS, visual analogue scale.



Medication	Months 0-3	Months 4-6	Months 7-9	Months 10-12	Overall Months 0-12
ACEi / ARB / ARNi	120 (0.18)	69 (0.10)	61 (0.10)	62 (0.11)	312 (0.12)
Betablockers	81 (0.12)	50 (0.08)	36 (0.06)	42 (0.07)	209 (0.08)
MR-Antagonists	70 (0.10)	37 (0.06)	35 (0.06)	28 (0.05)	170 (0.07)
Diuretics	453 (0.67)	244 (0.37)	191 (0.32)	180 (0.31)	1068 (0.42)

Figure 5 Cumulative number of medication changes 12 months post-sensor implant (shown as total count of medication changes per 3-month period and rates of change per patient-month for each drug class). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; MR, mineralocorticoid receptor.

associated with frequent HFHs, while decreasing PAP reduced HFH risk,[11] irrespective of LVEF.[15,16] Small changes in dPAP were shown to be associated with major changes in mortality risk.[12] For example, dPAP decreases of 3–5 mmHg after 6-month treatment were associated with a 19% to 30% reduction in mortality, whereas dPAP increases of 5 mmHg elevated mortality risk by 42.8%.[12] Similar average decreases in dPAP (−3.1 at 6 months and −4.6 at 12 months) in MEMS-HF suggest comparable pathophysiological interrelations.

The disease management intervention applied in MEMS-HF did not, by itself, reduce hospitalisations in the INH study,[19] which supports the concept that PAP-guided HF management contributed to reductions in outcome events beyond those achievable with remote clinical management alone. Only a randomised trial can disentangle the effects of two care strategies as concurrently applied in MEMS-HF. The efficacy of PAP-guided HF management using the CardioMEMS™ HF system is, therefore, being further evaluated in the randomised controlled Hemodynamic-GUIDEd management of Heart Failure trial (GUIDE-HF; NCT03387813).[24]

The CHAMPION trial was performed at US sites with locally established HF disease management programmes.[13,14] Before MEMS-HF, such facilities rarely existed in Germany and telemedicine was seldom applied in HF outpatients. Therefore, a study environment had to be created in which investigators were trained how to set post-implant alert thresholds and adjust them over time, with the goal of normalising PAP. Structured treatment algorithms ensured uniform HF management across sites, and training was offered to caregivers about how to interpret and manage ambulatory PAP trends. Patients were empowered to adhere to monitoring schedules and GDMT leading to improved self-care.[19] Under these circumstances, outcomes improved over the period of PAP-guided HF management in the vulnerable MEMS-HF participants.

Although MEMS-HF results suggest generalisability of haemodynamic-guided HF management beyond the US health system, durable 'real-life' success requires both commercially-available devices enabling detection of haemodynamic congestion when clinical decompensation may still be averted, and adequate monitoring frequency with appropriate caregiver training to translate monitoring information into actionable HF treatment modifications.[17] Professional coaching is also required to enable and motivate patients to follow therapeutic recommendations, and timely PAP reassessment must inform caregivers and patients whether the intervention was effective. The actionable sequence of daily PAP measurements by patients, weekly trend review by healthcare providers, targeted medical interventions and follow-up of treatment effects is necessary to fully exploit the potential of haemodynamic-guided HF management. Each element of this PAP-based care cycle is essential to success.[25]

Adequate financial coverage is also important for sustainable implementation. In the countries involved in the MEMS-HF study, remote management of HF patients is currently not reimbursed. This may become especially relevant when the need arises to prevent hospitalisation and reduce the requirement for patients to physically attend ambulatory follow-up as, for example, during the current COVID-19 pandemic.[26] Studies to support reimbursement policies are ongoing, facilitated by methodological and feasibility data from MEMS-HF.

Although improving PROs is an important therapeutic goal, there was a lack of information on the effects of PAP-guided HF management on patient well-being over longer periods of time. At enrolment, patients had poor baseline health status and mood, which significantly improved over time. The observational design of MEMS-HF limits conclusions from these findings because significant spontaneous improvements in PRO may occur early after HFH.[27] However, given the severity of HF at enrolment and the progressive nature of this disease, sustained improvements in PROs as observed in MEMS-HF would not be expected to occur spontaneously. For the first time, patients with baseline mPAP ≥35 mmHg were found to have greater improvements in PROs and greater concomitant reductions in mPAP compared to those with lower baseline mPAP. Furthermore, responder analysis revealed that KCCQ summary score improvements of ≥10 points were associated with significantly greater mPAP decreases. This identifies PAP as an important contributor to health status.

Additionally, MEMS-HF findings link depressive symptoms to a treatable biological variable, haemodynamic congestion, and corroborate their close interrelation with health status as assessed by the KCCQ.[19] This is relevant, because depression predicts poor outcomes in HF.[28] Across the entire sample, mPAP decreases were associated with significant, clinically relevant and lasting remission of depressive symptoms. Again, greater mPAP decreases were associated with greater decreases in the PHQ-9 depression sum score. These observations complement and expand previous reports, where PAP decreases were found to be directly associated with a lower risk of hospitalisation[11,13,14] and death.[12,16]

Limitations

A number of potential limitations must be considered when interpreting the MEMS-HF findings. Although helpful for evaluating safety and feasibility, prospective registries using historical events for within-patient comparisons cannot provide definitive effectiveness data. The post-implant changes in HFH observed in MEMS-HF support the concept that remote haemodynamic-guided HF management may be superior to clinical management strategies alone. However, the observed effect sizes must be viewed with caution. Several uncontrolled biases may have impacted the results, including information bias, regression to the mean, asymmetrical data handling, and confounding or selection of patients thought to be adherent to remote patient management requirements.

Elevated PAP was not an inclusion criterion in MEMS-HF. Since PAP is bound to zero, the opportunity to lower PAP increases as baseline PAP values increase. Per study protocol, only PAP levels above the pre-defined threshold range triggered physician alerts as a reminder to amend therapy, which implies that the greatest PAP lowering was achieved in patients with the highest baseline PAP. Typical regression to the mean would not be expected under these circumstances. Furthermore, MEMS-HF participants used the CardioMEMS™ HF system for daily automatic PAP measurement and transmission. PAP trends were then utilised by caregivers to guide HF management. This makes asymmetrical data

handling unlikely. Although the MEMS-HF study protocol did not request using information from right heart catheterisation during sensor implant, investigators might have considered these measurements to additionally inform HF management. Moreover, patients received disease management to complement PAP-guided care, which is not the current therapeutic standard in the countries where MEMS-HF was performed. It is possible that these factors reduced the frequency of PAP deviations requiring medication adjustments, but given that PAP monitoring does not *per se* constitute a treatment, it should not be subject to confounding directly. The CardioMEMS™ HF system is by nature a monitoring tool, and PAP changes were not the primary therapeutic goal in MEMS-HF. Rather, this system enables optimal HF management based on close surveillance of daily PAP values made available by patients themselves. Thus, patients' awareness of being observed (referred to as Hawthorne effect) constitutes an integral part of this care strategy. Treatment optimisation with the aim of reducing haemodynamic congestion and preventing clinical congestion relies on patients' willingness and ability to collaborate, which requires consideration of patients' motivation to undergo remote HF management prior to allocation of a CardioMEMS™ HF system.

Conclusions

The MEMS-HF study found that haemodynamic-guided HF management using an implanted PAP sensor is safe and feasible. Additionally, there was an association between haemodynamic-guided HF management and reductions in HFH. MEMS-HF results support the generalisability of this management approach, provided the necessary infrastructural resources are available. Furthermore, an association between the magnitude of PAP decreases and improvements in PROs was observed. Together, these findings add to evidence from randomised trial results and support the concept that active medication changes intended to lower remotely obtained PAP values have potential clinical benefit over remote clinical management alone and are feasible in HF outpatients with persistent NYHA class III symptoms following HFH. This approach might prove particularly valuable as virtual healthcare visits gain importance because it helps maintain effective outpatient management when personal contact is problematic.

Supplementary Information

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

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