Remote Haemodynamic Monitoring of Pulmonary Artery Pressures in Patients with Chronic Heart Failure (MONITOR-HF):

A randomised controlled clinical trial in a contemporary heart failure population

Brugts JJ MD[(1)]*; Radhoe SP MD[(1)]*; Clephas PRD MSc[(1)]'; Aydin D MD[(1)]'; van Gent MWF MD[(2)]; Szymanski MK MD[(3)]; Prof Rienstra M MD[(4)]; van den Heuvel MH MD[(5)]; da Fonseca CAF MD[(6)]; Linssen GCM MD[(7)]; Borleffs CJW MD[(8)]; Prof Boersma H MD[(1)]; Prof Asselbergs FW MD[(9)]; Mosterd A MD[(10)]; Prof Brunner-La Rocca HP MD[(11)]; Prof de Boer RA MD[(1)] for the MONITOR-HF investigators#.

*/' shared equal contribution; # group authorship: see listing table

[(1)] Erasmus MC University Medical Centre, Rotterdam, the Netherlands. [(2)] Albert Schweitzer Hospital, Dordrecht; [(3)] Utrecht University Medical Centre, Utrecht; [(4)] University Medical Centre Groningen, Groningen; [(5)] Medisch Spectrum Twente, Enschede; [(6)] Medisch Centrum Leeuwarden, Leeuwarden; [(7)] Hospital Group Twente, Almelo; [(8)] HAGA Hospital, Den Haag; [(9)] Amsterdam University Medical Centre; [(10)] Meander Medical Centre, Amersfoort; [(11)] Maastricht University Medical Centre, Maastricht.

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Address for correspondence:

Prof. dr. Rudolf A. de Boer MD PhD FESC FAHA

Department of Cardiology

Erasmus MC University Medical Centre,

Dr. Molewaterplein 50, 3015GD

Rotterdam, the Netherlands

Tel. : +31107047040

Email : r.a.deboer@erasmusmc.nl

ABSTRACT

Background: The effect of haemodynamic monitoring of pulmonary artery pressure has predominantly been studied in the USA. There is a clear need for randomised trial data from patients treated with contemporary guideline directed-medical-therapy with long-term follow-up in a different health-care system.

Methods: MONITOR-HF was an open-label, randomised trial, done in 25 centres in the Netherlands. Eligible patients had chronic heart failure of New York Heart Association class III and a previous heart failure hospitalisation, irrespective of ejection fraction. Patients were randomly assigned (1:1) to haemodynamic monitoring (CardioMEMS-HF system, Abbott Laboratories, Abbott Park, IL, USA) or standard care. All patients were scheduled to be seen by their clinician at 3 months and 6 months, and every 6 months thereafter, up to 48 months. The primary endpoint was the mean difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 months. All analyses were by intention-to-treat. This trial was prospectively registered under the clinical trial registration number NTR7673 (NL7430) on the International Clinical Trials Registry Platform.

Findings: Between April 1, 2019, and Jan 14, 2022, we randomly assigned 348 patients to either the CardioMEMS-HF group (n=176 [51%]) or the control group (n=172 [49%]). The median age was 69 years (IQR 61–75) and median ejection fraction was 30% (23–40). The difference in mean change in KCCQ overall summary score at 12 months was 7·13 (95% CI 1·51–12·75; p=0·013) between groups (+7·05 in the CardioMEMS group, p=0·0014, and –0·08 in the standard care group, p=0·97). In the responder analysis, the odds ratio (OR) of an improvement of at least 5 points in KCCQ overall summary score was OR 1·69 (95% CI 1·01–2·83; p=0·046) and the OR of a deterioration of at least 5 points was 0·45 (0·26–0·77; p=0·0035) in the CardioMEMS-HF group compared with in the standard care group. The freedom of device-related or system-related complications and sensor failure were 97·7% and 98·8%, respectively.

Interpretation: Haemodynamic monitoring substantially improved quality of life and reduced heart failure hospitalisations in patients with moderate-tosevere heart failure treated according to contemporary guidelines. These findings contribute to the aggregate evidence for this technology and might have implications for guideline recommendations and implementation of remote pulmonary artery pressure monitoring.

Funding: the MONITOR-HF trial is an investigator-initiated study funded by the Dutch Ministry of Health with the innovation grant 2018 by the Health Care Institute for conditional reimbursement. Abbott Laboratories (Illinois, US) was obligated to extend the grant by covering the clinical study costs with no part in the design, or conduct of the study or any of its components, analyses and/or writing.

Clinical Trial Registration number NTR7672

Research in Context

Evidence before this study: We searched PubMed for articles published in English and completed trials registered on ClinicalTrials.gov up to April 1, 2023, with the search terms “heart failure”, “pulmonary artery pressure sensor”, and “randomised clinical trial”. Our search identified two previous randomised trials (CHAMPION and GUIDE-HF). The CHAMPION trial randomly assigned 550 patients with New York Heart Association (NYHA) class III heart failure and previous heart failure hospitalisation irrespective of ejection fraction and showed a significant 28% reduction in heart failure hospitalisation at 6 months. The study was not powered for mortality. The GUIDE-HF trial included 1000 patients with NYHA class II–IV heart failure and increased N-terminal pro-B natriuretic peptide (NT-proBNP) concentrations or previous heart failure hospitalisation to broaden the range of eligible patients. The overall result was neutral but a prespecified COVID-19 analysis showed a significant benefit in reducing heart failure hospitalisation. The results of GUIDE-HF might have been related to the selected population having relatively low risk (mean ejection fraction of 40%, low pulmonary artery pressure, and NYHA class II) or additionally, by modification of the COVID-19 interaction. To date, no randomised data are available after the GUIDE-HF trial. Furthermore, trial data from a different health-care system other than that of the USA are absent, including data from trials with open-label access or comparison with a standard of care control group. As the current recommendation in the European Society of Cardiology heart failure guideline is for class IIb and pulmonary artery monitoring is not reimbursed, this has resulted in minimal uptake in Europe, so far, according to these aggregate data.

Added value of this study: Heart failure hospitalisations and mortality remain high among patients with heart failure. The MONITOR-HF trial is the first randomised clinical trial to investigate the benefits of pulmonary-artery-pressure-guided management in a European health-care system. Significant differences exist between Europe and the USA that are related to governance, financial and reimbursement strategies, as well as patient factors such as health-care insurance status and health-care access, and thresholds of hospital care availability. Studying a different health-care system in addition

to this single technology is thus of direct importance and can answer several remaining questions for regulatory agencies and payers. The Netherlands is known for its high quality of care, as exemplified by a comparison of the US CHAMP-HF and Dutch CHECK-HF registries. The MONITOR-HF trial showed an appropriate level of contemporary guideline directed-medical-therapy with high uptake of angiotensin receptor–neprilysin inhibitors and SGLT2-inhibitors. Additionally, this study provided detailed information about medication changes and natriuretic peptide concentrations from baseline to follow-up, elements that were lacking in previous trials that are important to study the effect of the intervention. This trial provides novel data with respect to quality of life of patients and heart failure hospitalisations.

Implications of all the available evidence: The findings of MONITOR-HF showed a consistent benefit of haemodynamic-guided care for patients with heart failure by substantially improving quality of life and reducing heart failure hospitalisations. The additive evidence of haemodynamic monitoring in addition to standard care in the Netherlands is also of interest for other European countries. The aggregate evidence from the three trials could affect guideline recommendations on the use of haemodynamic-guided management with pulmonary artery sensors and subsequent reimbursement programmes throughout Europe and beyond.

Introduction

Heart failure is a global health problem with high mortality and morbidity and is one of the leading causes of hospital admissions.[1] As hospitals run at full capacity, one of the biggest challenges is in relocating the delivery of care from a passive hospital-centred setting towards a proactive and remote patient-centred approach for a future-proof health-care system. The evidence of telemonitoring modalities for chronic heart failure is inconsistent and limited by the multiple and heterogeneous approaches.[2, 3] As haemodynamic congestion precedes overt clinical congestion4, invasive parameters could provide a more adequate monitoring target. Responding to haemodynamic congestion can lead to the accurate and timely diagnosis of worsening heart failure and an opportunity for early intervention with decongestive therapies to prevent heart failure hospitalisations, often without symptoms or signs of clinical congestion. This lack of symptoms or signs is probably why many non-invasive telemonitoring modalities fail to achieve this time window because the intervention is much later in the decompensation process.[2, 3, 4]

The CardioMEMS-HF system (Abbott Laboratories, Abbott Park, IL, USA) measures pulmonary artery pressure as a clinically intuitive and interpretable haemodynamic parameter and surrogate estimate of left-sided filling pressure.[4] Clinical evidence of remote monitoring with the CardioMEMS-HF system was provided by the CHAMPION trial[5] among patients with New York Heart Association (NYHA) class III heart failure. However, the subsequent GUIDE-HF trial[6] that aimed to test a broader patient population with NYHA class II–IV heart failure and either increased N-terminal-pro-B-type natriuretic peptide (NT-proBNP) concentrations or hospitalisation was inconclusive. The study was debated in a mostly statistical discussion and left the field with several questions. First, both trials were done in North America (predominantly in the USA, with a few sites in Canada). The value of pulmonary artery pressure monitoring in other health-care systems remains unknown, as the USA has a different health-care system, with a relatively lower adherence to guideline treatment but a higher rate of device implantation compared with western European countries, and a health-care structure

different to those of most European countries.[7,8,9] Second, GUIDE-HF was partially done during the COVID-19 pandemic, the follow-up was short and fixed at 12 months, and the control group received telephone calls at least once every 2 weeks, leaving several remaining questions.[6] Although some post-marketing approval studies confirmed the safety of the procedure and the reduction in heart failure hospitalisations with historical controls,[10,11] the aggregated trial evidence until now has resulted in a weak or uncertain recommendation for the CardioMEMS-HF system in the American Heart Association/American College of Cardiology 2022 and European Society of Cardiology 2021 heart failure guidelines: class IIb[12,13].

Therefore, there is a need for randomised trial data with additional geographical diversity as well as a call for an open-label trial using an actual standard of care control group to test another health-care system rather than a single technology[14]. Such data might shift the balance of aggregate evidence.

The MONITOR-HF randomised clinical trial investigated the effectiveness of remote haemodynamic monitoring in addition to standard care following contemporary treatment guidelines on quality of life (QOL) and heart failure hospitalisations in the Netherlands.[15]

Methods

Study design and participants

MONITOR-HF was a prospective multicentre (25 hospitals) open-label randomised clinical trial done in the Netherlands. The MONITOR-HF trial enrolled patients with NYHA class III chronic heart failure with a previous hospital admission for decompensated heart failure or urgent visit with the necessity of intravenous diuretics in the past 12 months, irrespective of left ventricular ejection fraction.[15] To be eligible for enrolment, patients with heart failure with reduced ejection fraction were treated with optimal or maximum tolerated treatment according to ESC guidelines, and evaluated for an implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy device (CRT) if indicated. The full inclusion and exclusion criteria are listed in the appendix (p 6). Further details on the design of the study and the rationale for an open-label study have been reported previously.[15] The research protocol and statistical analysis plan are provided in the appendix (pp 3–17).

Regulatory requirements, payers' justification, and patient councils played a role in choosing this design and control group. The protocol was approved by the central Medical Ethics Review Committee (METC-2018-1563) and all institutional review boards of the participating sites. All patients provided written informed consent, and the study was done in accordance with the Declaration of Helsinki. This trial was prospectively registered under the clinical trial registration number NTR7673 (NL7430) on the International Clinical Trials Registry Platform.

Randomisation and masking

We randomly assigned (1:1) participants to heart failure management with guideline directed medical therapy (GDMT) and diuretics (control group) or to heart failure management with GDMT and diuretics with the addition of haemodynamic monitoring by a pulmonary artery pressure sensor (CardioMEMS-HF group). Randomisation was done using a computer-generated schedule stratified by study site, with block sizes of 4 and 6 in random order. This trial was an open-label study (unmasked).

Procedures

Per protocol, patients allocated to the treatment group underwent sensor implantation within 3 weeks after randomisation. The implant procedure is described elsewhere.[15,16] All patients were instructed to take daily readings. The protocol defined treatment goals as decreasing pulmonary artery pressure when increased using diuretics, neurohormonal, or vasodilator drugs. Details of the readings, monitoring, and recommended response to increased pulmonary artery pressure are outlined in the appendix (pp 11–13). Briefly, titration of diuretics was recommended if the pulmonary artery pressure provided evidence of excess intravascular volume, and titration of vasodilators was recommended if increased vascular resistance was evident. In the control group, no implantation was performed and patients were managed with heart failure management with GDMT and diuretics on the basis of signs and symptoms, laboratory measurements, and echocardiography, without haemodynamic information, according to ESC guidelines. In the Netherlands, all participating sites had a dedicated outpatient clinic with nurses providing high-level background care (appendix p 11). All patients were scheduled to be seen by their clinician at 3 months and 6 months, and every 6 months thereafter. Follow-up was identical between groups. The last patient included was followed up for at least 12 months. The maximum follow-up was extended to 48 months. We collected adverse events (appendix p 8) and endpoint data throughout the follow-up period.

Outcomes

The primary efficacy endpoint was the mean change in Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores from baseline to 12 months between groups. The KCCQ is a 23-item, disease-specific measure that assesses the impact of heart failure according to a patient's perception of their health status. The KCCQ has been shown to be valid, reliable, and sensitive to clinical changes in patients with heart failure.[17,18,19] Scores range from 0 to 100, with higher scores reflecting better health status. KCCQs were administered by independent research personnel,

predominantly on paper, and were intensively monitored on adherence to study protocol and completeness during the study.

The secondary efficacy endpoint was the total number of heart failure hospitalisations (first and recurrent) and urgent visits with the necessity of intravenous diuretics during follow-up. A heart failure hospitalisation was defined as an unscheduled hospitalisation for heart failure longer than 6 h or the need for intravenous diuretics for decongestion of the patient. An urgent visit was additionally defined as an unscheduled hospitalisation for heart failure shorter than 6 h and the use of intravenous diuretics for decongestion of the patient. In the main analyses, total heart failure hospitalisation was defined as the composite of unscheduled heart failure hospitalisations and urgent visits with intravenous diuretics. Other secondary endpoints were the time-to-first-event analysis for first heart failure hospitalisation, the composite endpoints first heart failure hospitalisation and all-cause deaths, or the composite endpoint of first heart failure hospitalisation and cardiovascular death, as well as all-cause death and cardiovascular death, separately, and EQ-5D-5L visual analogue scale (VAS) and 6-min-walk test (6MWT) scores. A detailed medication logfile was obligatory and recorded for all patients including up-titrations and down-titrations of diuretics and changes in GDMT and diuretics during follow-up. A detailed patient contact logbook was recorded. The primary safety endpoints were device-related or system-related complications (DSRCs) and sensor failures.

Statistical analysis

The sample size calculation is described in detail elsewhere (appendix p 16).[15] A statistical power of 90% on mean change in KCCQ overall summary score of at least 6 (SD 15, α=0·05) was ensured if 266 patients were available for the primary endpoint analysis at 12 months.[15]

Within-group changes in mean KCCQ overall summary scores were assessed by paired Student's *t* tests. Differences in mean changes in KCCQ overall summary scores between the CardioMEMS-HF and control groups were then analysed using an unpaired *t* test (primary analysis). Subsequently, the

proportion of patients with at least a 5-point, 10-point, or 15-point improvement or deterioration in KCCQ overall summary scores (from baseline to 12 months) was measured, and differences in odds between the CardioMEMS-HF and control groups were analysed using logistic regression adjusted for the baseline value. To assess the effect of missing data on the KCCQ overall summary score at 12 months, we applied several sensitivity analyses (appendix p 14): we repeated these analyses on datasets in which the 6-month values were carried forward to the 12-month timepoint for those who had cardiovascular death after 6 months, for those who had all-cause death after 6 months, and for all participants with missing data after 6 months. We decided not to carry forward missing values before 6 months considering the timespan to the primary timepoint. Additionally, we tested the association using a linear mixed model for repeated measurements using all available datapoints of patients, which was used to calculate the longitudinal trend in changes in KCCQ overall summary scores between groups (appendix p 14). For clinical endpoint analyses, we applied the Andersen-Gill extension of the Cox regression model with the robust sandwich estimate of variance to relate randomly allocated treatment with total heart failure hospitalisations and the composite of total heart failure hospitalisations and all-cause deaths. Model assumptions for the described analyses were met. We did sensitivity analyses in prespecified strata according to age, sex, cause, ejection fraction below 40% and 40% or greater, diabetes of any type, atrial fibrillation, and device implant history (CRT or ICD). Additionally, in subgroup analyses, we studied the consistency of treatment effect by adding an interaction term between randomly allocated treatment and the corresponding stratum. The relationship between randomly allocated treatment and clinical endpoints was further studied by Cox proportional hazard regression models in time-to-first event analyses. Freedom of clinical endpoints was studied using the Kaplan-Meier method, whereas the log-rank test was applied to reveal differences between treatment groups. Additionally, censoring occurred in case of withdrawal, death, or end of follow-up. Other endpoints included the EQ-5D-5L questionnaire VAS and 6MWT scores. We analysed pulmonary artery pressure as the area under the pressure–time curve (AUC) of each patient's daily change in pulmonary artery pressure from baseline, calculated using the trapezoidal

rule. Using the medication and patient contact logbook, we calculated the average number of patient contacts per month and medication change rate per patient-month. All analyses were based on the intentionto-treat principle (from date of enrolment, regardless of receiving allocated treatment) for the entire follow-up period. Clinical endpoints were additionally analysed in the per protocol analysis (appendix p 15). No crossover between groups was allowed.

The statistical analysis plan was updated to include a COVID-19 sensitivity analysis before the last follow-up visit on January 31, 2023 (appendix p 17). This COVID-19 sensitivity analysis showed no interaction of COVID-19 warranting no stratified analysis or presentation of results (appendix p 19).

An independent data safety monitoring board (DSMB) reviewed all available safety and clinical event data. The DSMB regularly reviewed accumulating trial data and advised the sponsor regarding the continued safety, validity, and scientific merit of the trial. An independent unexpected serious-adverse device effect committee was installed to assess relatedness of adverse events to the device or implant procedure. An independent blinded clinical event classification committee reviewed and adjudicated all deaths, unscheduled hospitalisations, and urgent visits with the use of intravenous diuretics.

Role of the funding source

The investigator-initiated study was designed and undertaken by the Erasmus MC University Medical Centre (clinical research organisation and sponsor). Data were monitored, collected, and managed by the sponsor. The study was funded by the Dutch Ministry of Health and National Health Care Institute as conditional coverage programme for innovations in health care. Abbott Laboratories (IL, USA) was obligated to extend the grant by covering the clinical study costs with no part in the design, or conduct of the study or any of its components, analyses or writing.

Results

Between April 1, 2019, and Jan 14, 2022, we randomly assigned 348 patients to either the CardioMEMS-HF group (n=176 [51%]) or the control group (n=172 [49%]; figure 1). The last patient completed follow-up on Jan 31, 2023. The mean follow-up time was 1·8 years (SD 0·9). The groups were similar in terms of baseline characteristics (table 1).

Patients in both groups had similar mean baseline KCCQ overall summary scores (55·8 [SD 23·3] in the CardioMEMS-HF group and 54·9 [22·3] in the standard care group; p=0·70; table 2). The mean change in KCCQ overall summary scores between baseline and 12 months among patients in the CardioMEMS-HF group was +7·05 (95% CI 2·77 to 11·33; p=0·0014), compared with –0·08 points among those in the standard care group (–3·76 to 3·60; p=0·97; table 2). Hence, the difference in the change in KCCQ overall summary score from baseline to 12 months was 7·13 (1·51 to 12·75; p=0·013) in favour of CardioMEMS-HF (table 2). The KCCQ-scores for all six domains are presented in figure 2. In the responder analysis, the proportions of patients with an improvement in KCCQ overall summary score by at least 5 points were 47·7% in the CardioMEMS-HF group and 38·1% in the standard care group (odds ratio [OR] of 1·69 [95% CI 1·01 to 2·83]; p=0·046). The proportions of patients with a deterioration in KCCQ overall summary score by at least 5 points were 24·2% in the CardioMEMS-HF group and 39·5% in the control group (OR 0·45 [0·26 to 0·77]; p=0·0035; table 2; figure 3). Missing data were equally distributed between groups and the favourable effect of CardioMEMS-HF on the mean change in KCCQ overall summary score and the responder analysis was confirmed and consistent in all sensitivity analyses for missing data (appendix pp 20–22).

The total number of heart failure hospitalisations was 117 in the CardioMEMS-HF group and 212 in the control group, which corresponded to an event rate of 0·381 per patient-year in the CardioMEMS-HF group and 0·678 per patient-year in the control group. Hence, the rate of total heart failure

hospitalisations was reduced by 44% (hazard ratio [HR] 0·56 [95% CI 0·38–0·84; p=0·0053; table 2; figure 4). Data on other clinical endpoints are presented in table 2. The numbers of patients that were admitted for heart failure hospitalisation within 4 weeks after randomisation were seven (4%) in the CardioMEMS-HF group and 14 (8%) in the standard care group (p=0·41). No significant effect on deaths was observed. The number of non-heart failure-related admissions was not different between randomised groups (129 in the CardioMEMS group versus 132 in the Standard Care group). Additionally, we did an analysis of heart failure hospitalisations excluding the urgent visits (appendix p 25); did prespecified subgroup analyses, which showed an overall consistent treatment effect but a potential signal of heterogeneity with a more pronounced effect in non-ischaemic cardiomyopathy (appendix p 26); and did a separate per protocol analysis with similar results (appendix p 27). In the per-protocol analysis, the HR of total heart failure hospitalisation was 0·56 (0·37–0·84; p=0·0048) and the HR for time-to-first event heart failure hospitalisation or all-cause death was 0·72 (0·53–0·97; p=0·029; appendix p 27). The Kaplan Meier figures for clinical endpoints are presented in the appendix (pp 36–38).

The mean pulmonary artery pressure at baseline was 33·3 mm Hg (SD 10·6) in patients in the CardioMEMS-HF group, which was increased above normal. The mean pulmonary artery pressure was significantly reduced to 24·9 mm Hg (SD 9·4) at 12-month follow-up (p<0·0001). The mean pulmonary artery pressure AUC, used to express the reduction in pulmonary artery pressure over time, was substantial with –1623·8 mm Hg-days (SD 2003·4; figure 5; appendix p 39). The median NT-proBNP was significantly reduced from 2377 pg/mL at baseline to 1708 pg/mL (p=0·013) at 12 months in the CardioMEMS-HF group. In the standard care group, we found a non-significant difference in NT-proBNP (1907 pg/mL to 1607 pg/mL, p=0·81) at 12 months (figure 5). The baseline treatment level and mean dose as a percentage of the target dose was appropriate among all patients and the uptake of angiotensin receptor–neprilysin inhibitors (ARNIs) and SGLT2-inhibitors was

substantial (table 1; appendix pp 28–30). The cumulative number of changes, intensifications, and downgrades in diuretics and GDMT were higher in the CardioMEMS-HF group than in the control group (figure 6; appendix pp 40–47). The mean number of patient contacts per month was 1·55 (SD 1·06) in the CardioMEMS-HF group and 1·04 (0·77) in the control group during the entire follow-up period (appendix p 31), and the rate of medication changes per patient-month was 0·93 in the CardioMEMS-HF group and 0·55 in the standard care group during the 12-month follow-up (appendix p 31). The mean difference in EQ-5D-5L VAS score from baseline to 12 months between groups was 6·0 (95% CI 1·1 to 10·9; p=0·016) in favour of CardioMEMS-HF (+3·0 in the CardioMEMS-HF group and –3·0 in the control group). The mean 6MWT scores from baseline to 12 months significantly improved by 29·3 m (2·4 to 56·2; p=0·033) in the CardioMEMS-HF group but not in the standard care group (9·8 m [–20·4 to 40·1]; p=0·52). In exploratory analyses, improvements in KCCQ overall summary scores in the CardioMEMS-HF group were positively associated with an improvement in 6MWT distance, EQ-5D-5L VAS score, and NYHA class (appendix p 33). Frequency of (daily) pulmonary artery uploads was 84·3% during follow-up. The freedom of DSRCs was 97·7% (DSRC occurred in four [2·3%] of 172 implants) and freedom of sensor failures was 98·8% (sensor failure in two [1·2%] of 168 active sensors; appendix p 34). In four (2%) patients, a device-related complication occurred (two haemoptysis and two arrhythmia requiring invasive measures; appendix p 34).

Discussion

The MONITOR-HF study showed that haemodynamic monitoring and subsequent individualised adjustment of diuretics and GDMT significantly improved QOL and reduced the number of heart failure hospitalisations.

The MONITOR-HF is the first randomised clinical trial of haemodynamic monitoring in Europe and considered both QOL and recurrent heart failure hospitalisations. The QOL improvement was substantial considering that it represents group levels and persisted until 12 months. The control group exhibited no change in QOL. Additionally, the reduction in heart failure hospitalisations was substantial. Given the enormous burden of heart failure on hospitals, such profound reductions portend an important tool to keep patients ambulatory as long as possible.

Two randomised trials[5,6] have studied the effect of haemodynamic pulmonary-artery pressure monitoring on chronic heart failure. Our results are consistent with the findings of the CHAMPION trial. However, because CHAMPION recruited patients well over a decade ago, we saw a much higher level of GDMT and contemporary standard care in our study.[5] Essentially, the MONITOR-HF trial showed one of the highest uptakes of ARNIs and SGLT2-inhibitors in trials to date, and the use of mineralocorticoid receptor antagonists was also much higher in this trial than in most other trials. The added value of remote monitoring in our study cannot therefore be ascribed to relatively lower levels of GDMT in standard care patients, a potential reason that was discussed after the CHAMPION findings.[5] As mentioned, the results of the GUIDE-HF trial, predominantly from the USA, were inconclusive but positive in the prespecified COVID-19 analysis.[6] Our trial results support the benefit of haemodynamic monitoring, which is consistent across the three trials. The health-care systems of Europe and the USA are substantially different.[7,8,9] It is reassuring that the results of the three trials are highly concordant and robust in a new setting.[14,21]

A particular strength of our trial was the consistency between crucial elements of a remote monitoring approach. We reported a prominent effect on pulmonary artery pressure, accompanied by a clear decrease in natriuretic peptide concentrations associated with increased changes, especially in diuretics, but also in other guideline-directed treatments, among patients allocated to remote monitoring. To better understand the mechanism of benefit of pulmonary artery pressure-guided therapy we report in detail on drug changes. The added benefit of haemodynamic monitoring is shown

by the apparent optimisation of the congestive state of patients, with fine-tuning of drug doses.[21] In GUIDE-HF, the smaller effect on mean pulmonary artery pressure and a low baseline level of pulmonary artery pressure as compared with our study was observed, which probably limited the possibility of improvement.[6] Our results showed a substantial reduction in mean pulmonary artery pressure from baseline and a mean response that was higher than those in previous trials. In finding the optimal opportunity for haemodynamic monitoring to make an impact, these differences are noteworthy.

Chronically better congestive status and proactive response to increases in pulmonary artery pressure prevent worsening heart failure progressing to overt clinical congestion requiring hospitalisation.[22] Remote monitoring must be followed by an adequate telemonitoring platform structure. The monitoring device itself does not treat the patient, and its effects are conceded by optimising diuretics in response to pressure and titration of drug treatment.[21,22] Patient compliance with the technique was high, but also presents a potential vulnerability. Importantly, clinicians often need to actively intervene in an asymptomatic haemodynamically congested patient without clinical congestive symptoms. Training is needed to set the right thresholds and alarms for effective monitoring. As stated by Cleland and colleagues,[14] "to master heart failure, first master congestion"; no invasive tool will improve patients without acting on pressures. Clearly, remote monitoring triggered this interaction between patient and caregiver as reflected in the number of drug changes that primarily targeted fluid status and the decline in mean pulmonary artery pressure and natriuretic peptide concentration. Most changes were made in diuretics, which could be in both directions, up-titration in case of hypervolaemia and down-titrations in case of hypovolaemia in a safe and controlled way.

We acknowledge the limitations of an open-label design, as well as the absence of a device (or sham) in controls, which can be prone to bias in the QOL endpoint by unmasking. Unmasking might have negated any possible placebo effect of a device in the control group and by contrast might have enhanced any placebo effect in the treatment group. In GUIDE-HF, both groups improved in KCCQ

overall summary scores without significant difference between groups at 12 months. Still, the level of consistency and magnitude of the observed effects at multiple levels, including several supportive objective measures (pulmonary artery pressure, natriuretic peptide concentrations, and clinical endpoints) and that the control group had highly appropriate background therapy and identical follow-up scheme, minimised the chances of imprecisions or bias in our study and brings novel data. Furthermore, by contrast with GUIDE-HF, in which control patients were called every 2 weeks, in MONITOR-HF standard care was given at outpatient clinics, and we believe that the control group better represented actual standard care practice in outpatient clinics for the first time. Moreover, because this is the first trial without a sham procedure in the control group, our analyses allowed for discrimination in QOL changes between the CardioMEMS-HF group and a standard care group who did not receive the device. CHAMPION did not assess KCCQ scores but showed an improvement in Minnesota Living with HF Questionnaire scores, whereas in GUIDE-HF KCCQ overall summary scores improved in both groups equally.[5,6] In our study, only CardioMEMS-HF patients improved in KCCQ-OS score and patients in the control group had no overall change in QOL. Although the trial was randomised and adequately powered for QOL, we analysed missing data with various methods that did not affect the main inferences and results. Furthermore, trials of established guideline treatments such as ARNIs and SGLT2-inhibitors showed effects in the range of one-point or two-point differences in KCCQ overall summary scores between treatment groups.[23,24,25] We observed potential heterogeneity with respect to heart failure cause with a more pronounced effect in patients with non-ischaemic than with ischaemic heart failure; however, this difference was not observed in GUIDE-HF in a larger sample size and might be related to chance. The effect of the COVID-19 pandemic on our trial was modest, and most of the study was done during the COVID-19 pandemic over a long time-span from 2019–23, which might explain the smaller effect of COVID-19 on our results as compared to GUIDE-HF (2018–21), in addition to differences in health-care systems, vaccination campaigns, differences in patient population, and the fixed follow-up at 12 months. Finally, we acknowledge that the implant procedure is not without risks or complications and the current study was not powered for

mortality. Given the small relative risk reductions in deaths, a larger sample size and longer follow-up could be needed for any effect to become apparent; patients who died early in the study could have obscured the full benefit of this technique (with chronically better fluid state) in relation to fewer deaths in the longer term.

Our results might support the heart failure community to embrace e-health, digital technology, and telemonitoring to reduce the burden on our hospitals. The process behind any telemonitoring modality needs a substantial workforce of health-care providers working with uniform signals, thresholds, and alarms for an effective implementation of patient monitoring. With optimal choices of thresholds, the workload is minimal, and one only actively responds to alarms outside the chosen threshold. With the upscaling of haemodynamic monitoring, the projected change in activities of staff should be appropriately reimbursed as well, which will be relevant for subsequent cost-effectiveness analyses.26 From available data, we will need to assess which patients are most likely to benefit in what stage of their disease, as existing invasive monitoring strategies are expensive and cannot be available for all patients. Other telemonitoring modalities such as simple non-invasive modalities might be better suited for patients at lower risk, those with less symptomatic heart failure, and those requiring a lower level of guidance considering the sheer number of patients with chronic heart failure worldwide.[2,3,27,28] Important future directions for upscaling can include developing centralised telemonitoring platforms. Some automatisation based on artificial intelligence algorithms could be integrated into digital platforms. Finally, we must involve the patients themselves to close the circle. Patients can play an active role in self-management, self-care, and awareness of the underlying disease. Apps can be developed to integrate pulmonary artery pressure feedback, lifestyle, fluid balance, and medication compliance with bidirectional remote contact with their caregiver. A structured care system, dedicated personnel, and patient involvement could create a synergistic effect of remote monitoring. Future research and resources on this topic are warranted.

The current study bridges several remaining gaps in knowledge after the previous two landmark trials. The aggregate results of haemodynamic monitoring in addition to standard care now show a consistent treatment benefit across three positive trials. The concordance on outcomes in these trials done in different eras, evolving GDMT, different conditions (pandemic vs non-pandemic) and different health-care systems and controls is remarkable. The average number of medication changes per month and patient contacts were also similar across the three trials. The differences in design of the three trials complement each other and extend the level of aggregated evidence for the use of pulmonary artery pressure-guided therapy.

Within Europe, hospital systems and organisation of care also vary between countries. The high level of GDMT in controls is one of the strongest points of our study and underlines the beneficial effects of pulmonary artery pressure monitoring in addition to high-quality usual heart failure care as comparator. The main intervention was through fine-tuning of diuretics and pertaining a chronically better decongestive state with haemodynamic monitoring. Despite the high standard of care and specific organisational structure in the Netherlands, optimisation and proactive interventions in volume status with diuretics made a clear impact on heart failure hospitalisation. Better decongestion and proactive responses to pressures triggered a remote interaction between patient and caregiver with optimisation of drug treatment that we postulate to be most likely generalisable to other European countries to prevent hospitalisations, despite differences between countries.

In summary, the MONITOR-HF trial is the first randomised clinical trial in Europe to show that haemodynamic monitoring and subsequent individualised modification of diuretics and GDMT substantially and significantly improve QOL and reduce the number of heart failure hospitalisations among patients with chronic heart failure.

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Contributors

SPR, PRDC, and DA contributed to data analyses. JJB, SPR, PRDC, DA, EB, RAdB contributed to interpretation of design, data analyses, methodology, interpretation, and writing the report. All authors contributed to data collection and provision of patients. All authors reviewed the data analyses, data interpretation, and writing of the report. All authors had full access to the study data and vouch for fidelity to the protocol and completeness and accuracy of the data, analyses, and results. All authors approved the final version of the submitted report and agreed for the decision to submit the manuscript.

Data sharing

No aggregate or patient-level data collected in this trial can be made available externally owing to internal regulations, patient consent and data-regulations for outside Erasmus Medical Center. Yet, researchers interested in collaboration should contact the corresponding author. The research protocol and statistical analysis plan are provided in the Supplementary Appendix. The design article of MONITOR-HF is published open-access in 2019[15].

Declaration of interests

JJB received an independent research grant from Abbott for investigator-initiated studies to the hospital and reports speaker engagement or advisory board fees from Astra Zeneca, Abbott, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Novartis, and Vifor. CAdF received consulting or speaker fees from Astra Zeneca, Abbott, Boehringer Ingelheim, Novartis, Pfizer, Bristol Myers Squibb, Philips, and Servier. CJWB served on advisory boards, or had speaker engagements with Abbott, AstraZeneca, Boehringer Ingelheim, and Novartis. HPB-LR reports unrestricted research grants from Vifor, Novartis, and Roche Diagnostics, and reports consultancy fees and payments for lectures from Vifor, Novartis, Boehringer Ingelheim, AstraZeneca, and Roche Diagnostic. RAdB has received research grants or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. All other authors declare no competing interests.

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Table 1

Baseline characteristics of study population

	CardioMEMS (N=176)	**Standard Care (N=172)**
Age, median (IQ)	69 (61-75)	70 (61-75)
Male sex (%)	138 (78·4%)	125 (72·7%)
Female sex (%)	38 (21·6%)	47 (27·3%)
Body Mass Index (kg/m^2), median (IQ)	27·2 (24·4-31·6)	26·8 (24·1-31·0)
Medical history		
Previous MI, %	81 (46·0%)	65 (37·8%)
Previous PCI, %	74 (42·0%)	59 (34·3%)
Previous CABG, %	34 (19·3%)	34 (19·8%)
Diabetes, %	66 (37·5%)	68 (39·5%)
CVA or TIA, %	29 (16·5%)	39 (22·7%)
Atrial fibrillation, %	100 (56·8%)	81 (47·1%)
Hypertension, %	102 (58·0%)	98 (57·0%)
Months since last HFH, median (IQ)	3·6 (1·2-6·4)	3·4 (1·6-6·7)
Years since HF diagnosis, median (IQ)	3·4 (0·8-8·3)	3·8 (0·9-8·7)
Etiology, ischemic, %	93 (52·8%)	81 (47·1%)
Heart rate, beats/min, median (IQ)	71 (64-81)	71 (64-80)
Systolic BP (mmHg), median (IQ)	112 (103-129)	115 (104-131)
Diastolic BP (mmHg), median (IQ)	68 (60-75)	68 (61-76)
LVEF, median (IQ)	30 (23-40)	30 (22-43)
- EF <40% (n)	127 (72·7%)	123 (71·5%)
- EF ≥40% (n)	48 (27·3%)	49 (28·5%)
Serum creatinine (umol/l), median (IQ)	127 (103-163)	124 (99-150)
eGFR (ml/min), median (IQ)	48 (35-60)	48 (38-63)
Chronic Kidney Disease (eGFR<60), %	131 (74·4%)	121 (70·3%)
NT-proBNP (pg/ml), median (IQ)	2377 (837-5153)	1905 (691-4444)
ICD, %	94 (53·4%)	102 (59·3%)
CRT, %	46 (26·1%)	46 (26·7%)
Medical therapy		
Beta-blocker, %	150 (85·2%)	142 (82·6%)
RAASi, %	154 (87·5%)	147 (85·5%)
ACEi, %	37 (21·0%)	32 (18·6%)
ARB, %	26 (14·8%)	26 (15·1%)
ARNi, %	81 (46·0%)	81 (47·1%)
Hydralazine dinitrate, %	10 (5·7%)	8 (4·7%)
MRA, %	143 (81·3%)	144 (83·7%)
SGLT2 inhibitor, %	12 (6·8%)	21 (12·2%)
Loop diuretic, %	168 (95·5%)	167 (97·1%)
Thiazide diuretic, %	11 (6·3%)	10 (5·8%)
Loop and thiazide diuretic, %	11 (6·3%)	10 (5·8%)
Ivabradin, %	14 (8·0%)	10 (5·8%)
Digoxin, %	44 (25·0%)	39 (22·7%)

All p-values for differences between randomised groups were non-significant.
All analyses based on intention-to-treat.

IQ = inter-quartile range, BP = blood pressure, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery, CVA = cerebrovascular accident, TIA transient ischemic attack, LVEF = left ventricular ejection fraction, EF = ejection fraction, GFR = glomerular filtration rate, ICD = intrinsic cardiac defibrillator, CRT = cardiac resynchronization therapy, RAAS = renin-angiotensin-aldosterone system, ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker,

ARNI = angiotensin-receptor neprilysin inhibitor, MRA = mineralocorticoid receptor antagonist, SGLT2 = sodium glucose cotransporter-2. HFH = heart failure hospitalisation.

Table 2

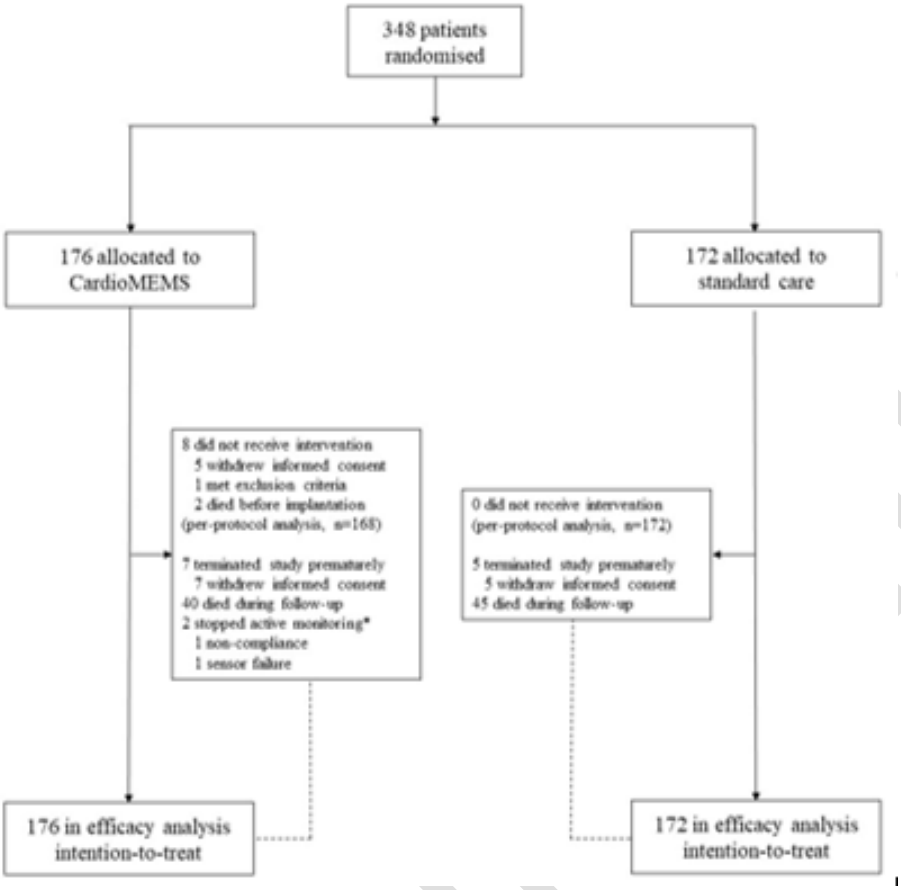
Primary endpoint and clinical outcomes in patients randomised to CardioMEMS and standard care during follow-up

	CardioMEMS	Standard Care		
	Within group	**Within group**	**Between groups**	**p**
Baseline KCCQ-OS score (mean, SD)	55·8 (23·3)	54·9 (22·3)	0·96 (-5·77-3·86)	0.697
12 months KCCQ-OS score (mean, SD)	66·1 (25·4)	56·9 (24·2)	9·19 (3·33-15·05)	0.002
Mean difference KCCQ-OS (mean diff., 95% CI**) at 12 months**	7·05 (2·77-11·33)	-0·08 (-3·76-3·60)	7·13 (1·51-12·75)	0·013
Responder analysis KCCQ-OS at 12 months	**N, %**	**N, %**	**OR (95% CI)**	**p**
≥15 points deterioration	21 (15·9%)	32 (21·8%)	0·65 (0·35-1·20)	0·139
≥10 points deterioration	24 (18·2%)	44 (29·9%)	0·49 (0·28-0·88)	0·015
≥5 points deterioration	32 (24·2%)	58 (39·5%)	0·45 (0·26-0·77)	0·003
≥5 points improvement	63 (47·7%)	56 (38·0%)	1·69 (1·01-2·83)	0·046
≥10 points improvement	55 (41·7%)	45 (30·6%)	1·85 (1·09-3·15)	0·020
≥15 points improvement	44 (33·3%)	31 (21·1%))	2·27 (1·26-4·08)	0·011
Clinical endpoints during follow-up				
	Events (rate/pt.yr)	**Events (rate/pt.yr)**	**HR (95% CI)**	**p**
Total HF hospitalisations	117 (0·381)	212 (0·678)	0·56 (0·38-0·84)	0·005
Total HFH and all-cause mortality	159 (0·518)	257 (0·822)	0·63 (0·44-0·90)	0·011
Urgent visits only	11 (0·036)	17 (0·054)	0·65 (0·23-1·88)	0·440
Time-to-first HFH	63 (0·254)	85 (0·395)	0·67 (0·49-0·93)	0·017
Time-to-first HFH, urgent visit or CV mortality	71 (0·286)	91 (0·423)	0·71 (0·52-0·97)	0·032
Time-to-first HFH, urgent visits all-cause mortality	81 (0·327)	98 (0·455)	0·75 (0·56-1·01)	0·054
CV mortality	25 (0·081)	31 (0·099)	0·83 (0·49-1·39)	0·485
All-cause mortality	42 (0·137)	45 (0·144)	0·96 (0·63-1·46)	0·846

Mean follow-up 1·78 years (SD 0·9). Total HFH is the composite of HF hospitalisation and urgent visits as outlined. HFH = Heart Failure Hospitalisation, n = number, HR = hazard ratio, CI = confidence interval, KCCQ= Kansas-City-Cardiomyopathy-Questionnaire, OS= overall summary score, p=p-value. All analyses based upon intention-to-treat.

Figure 1

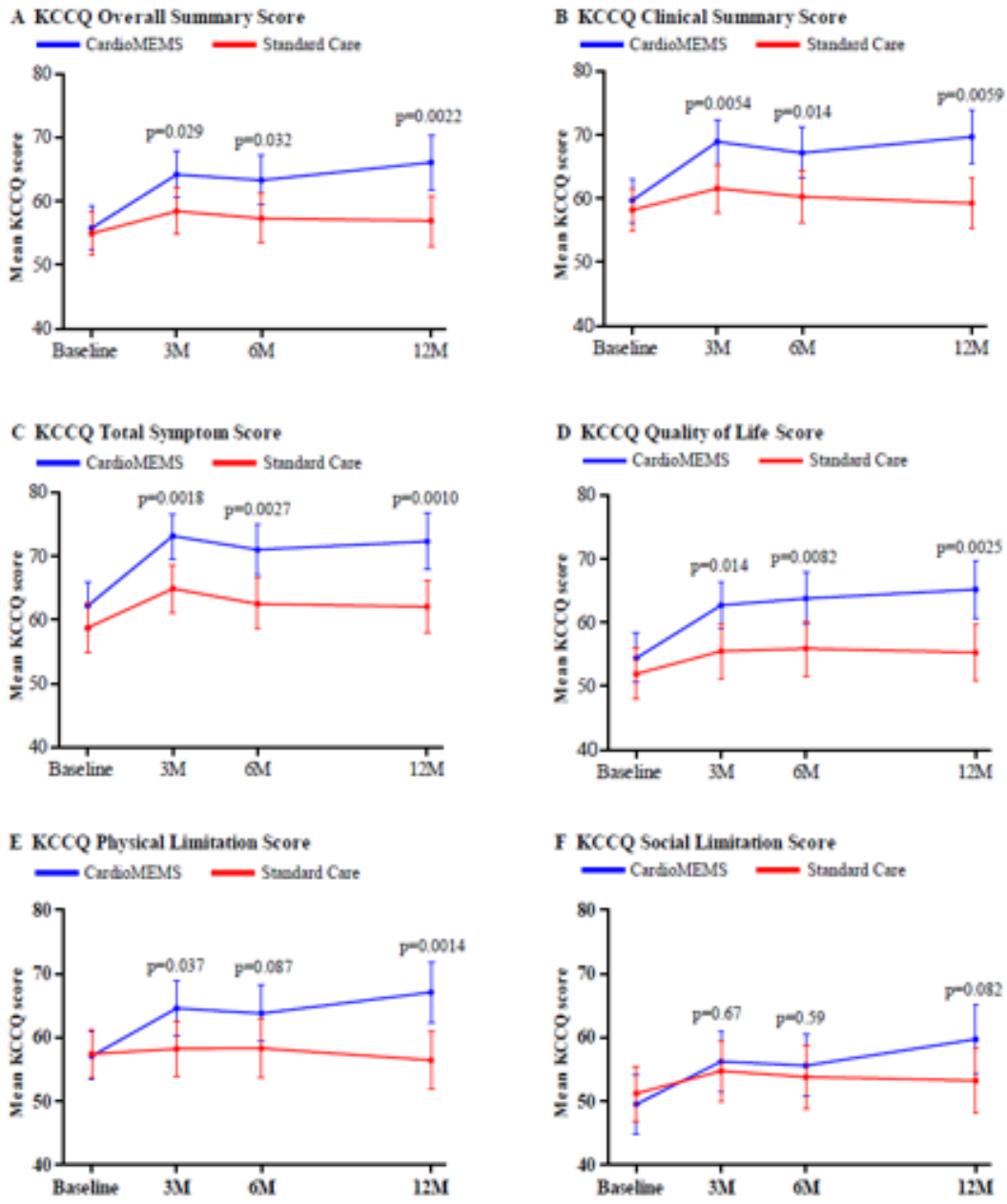
Trial profile



*Legend: the intention-to-treat (ITT) analysis population consists of all patients at the date of signed informed consent / randomization. Active treatment was available in 168 patients (per protocol analysis) with implanted CardioMEMS. * during follow-up 2 patients stopped active monitoring (1 non-compliance; 1 sensor failure without restoring signal) but both were contained in the active study follow-up. In the safety-analysis, 168 patients received a 1st implant attempt and 4 patients were included where a 2nd attempt was necessary after unsuccessful 1st attempt (2.3%) (see annex, safety data), all 2nd attempts were successful.*

Figure 2

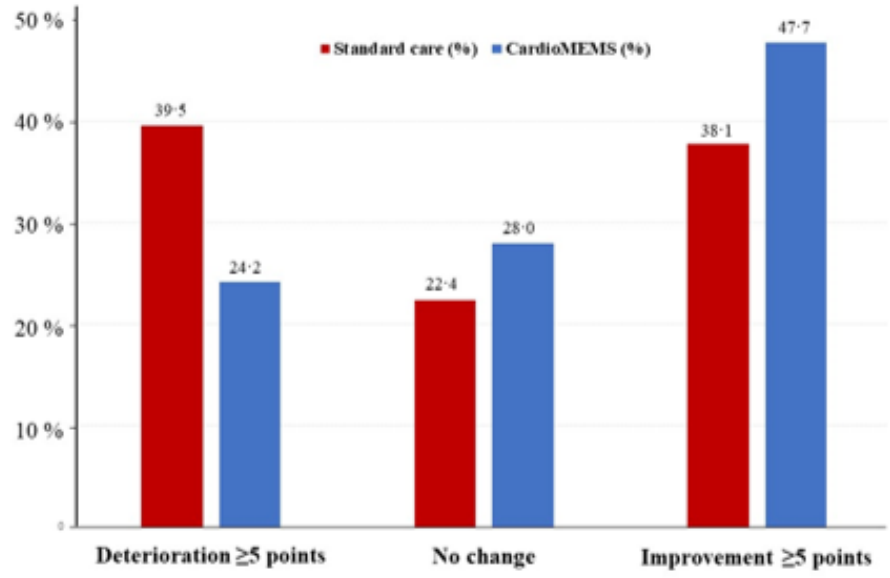
Mean KCCQ scores domains during follow-up in both randomised arms



Legend: KCCQ = Kansas-City-Cardiomyopathy Questionnaire, validated quality of life questionnaire in heart failure patients. On the x-axis the time points of assessment from baseline, 3 months, 6 months and 12 months. On the Y-axis the mean score per domain. In blue CardioMEMS and in red standard care patients. P-value are presented at each time moment for the difference between groups. The KCCQ contains 6 domains with plotted mean values of both treatment arms. OS = overall summary score, CS = clinical summary score, TSS = total symptom score, QLS quality of life score, PLS physical limitation score, SLS social limitation score.

Figure 3

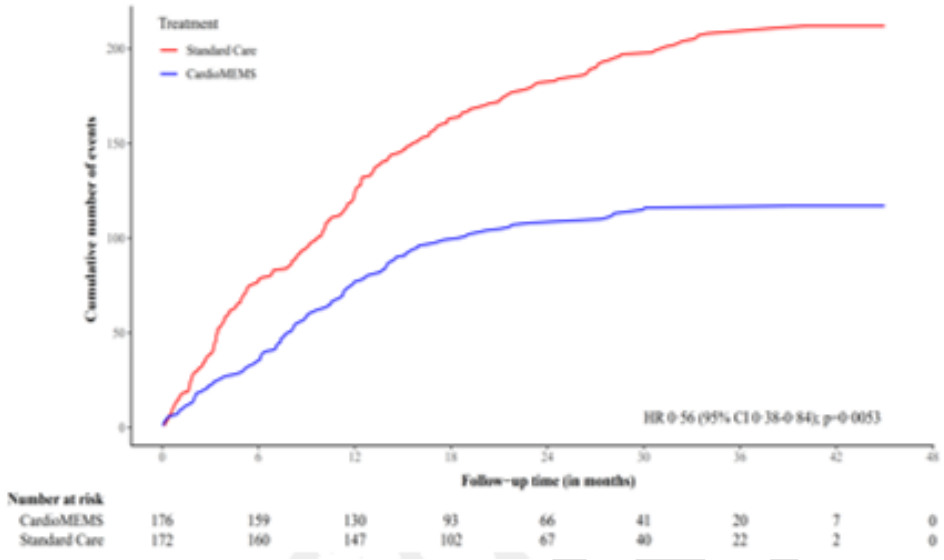
Responder analysis: proportions of patients with improvement or deterioration in quality of life as measured by the change in KCCQ-OS at 12 months



Legend: The responder analysis of KCCQ overall summary scores at 12 months with the proportion of patients (%) on the Y-axis and the categories of change on the X-axis, reading no change or improvement / deterioration of ≥5 points. Standard care in red bars, CardioMEMS in blue bars. P-value chi-square for difference of categories 0.022.

Figure 4

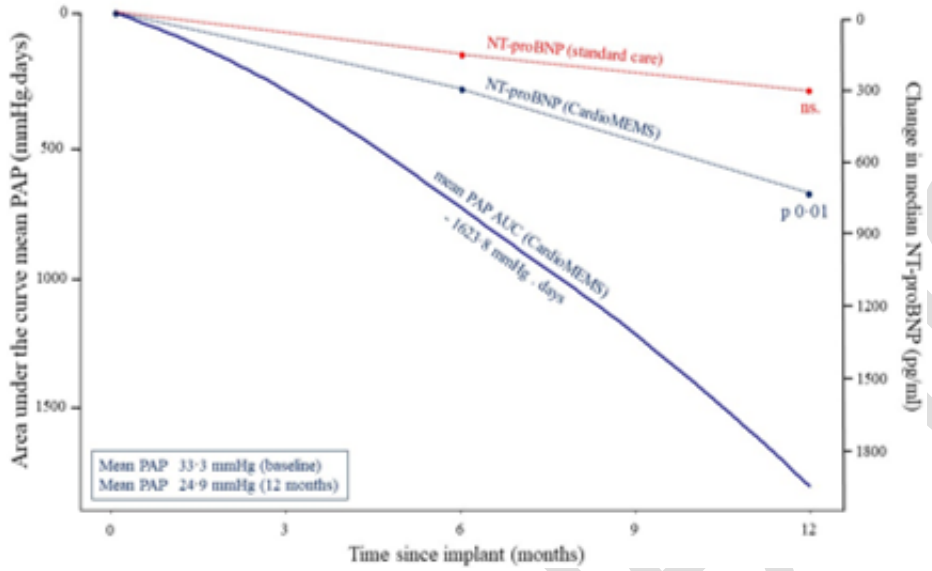
Cumulative HF-hospitalizations and urgent visits with IV diuretics among patients randomised to CardioMEMS or standard care during entire follow-up



Legend: The x-axis reads the follow-up time in months, the y-axis the cumulative number of total HFH events. In red standard care and in blue CardioMEMS patients.

Figure 5

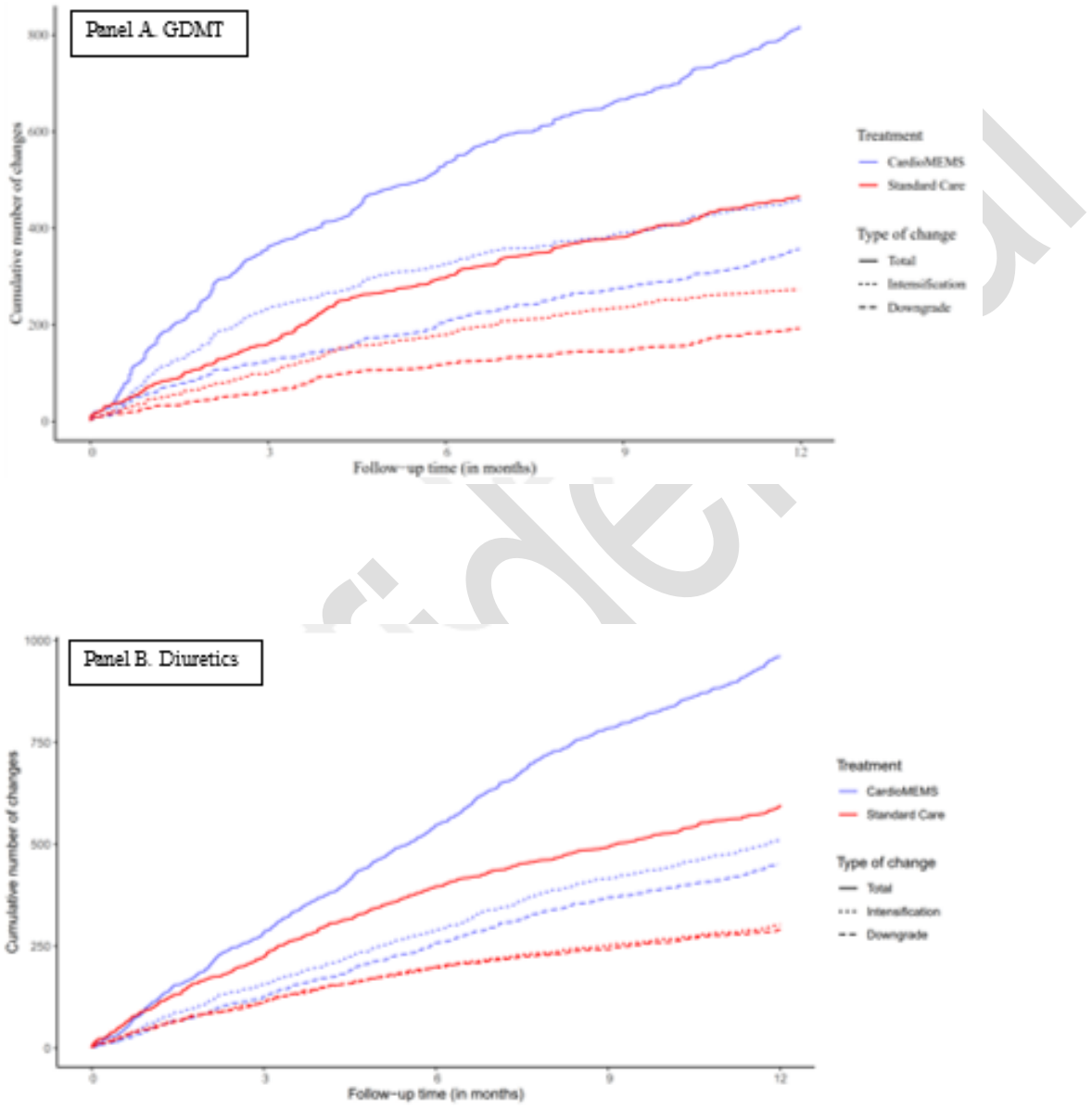
Mean Pulmonary Artery Pressure area under the curve and Natriuretic Peptides concentrations from baseline to 12 months follow-up.



Legend: Baseline mean PAP calculated as the mean of days 0-7-, and 12-months follow-up as mean PAP of days 358-365. The mean pulmonary artery pressure AUC is – 1623.8 (SD 2003,4) mm Hg-days in the treatment group. Change in median NT-proBNP is plotted with standard care in red dotted line (red) and CardioMEMS in blue dotted line (blue), described in results section; PAP = pulmonary artery pressure. AUC = area under the curve.

Figure 6

Cumulative number of drug changes, intensifications and downgrades in GDMT (panel A) and diuretics (panel B) in both treatment arms



Legend: On the x-axis is presented the follow-up time from baseline to 12 months, on the y-axis is presented the cumulative number of changes in GDMT (A) or diuretics (B). The dotted lines represent patients with standard care and the straight lines patients with CardioMEMS. The colors are for cumulative/total (red); intensifications (green) with up-titrations and/or starts, and downgrades (blue) with down-titrations and/or stops.