Remote haemodynamic-guided care for patients with chronic heart failure: a meta-analysis of completed trials

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**Aims**
Haemodynamic-guided heart failure (HF) management using directly measured cardiac filling pressures in symptomatic patients is now recommended in the European Society of Cardiology (ESC) Heart Failure Guidelines [Class IIb(B)]. This meta-analysis evaluates all data from completed clinical trials evaluating this approach in patients with HF.

**Methods and results**
All trials evaluating the impact of HF management based on haemodynamic monitoring using implantable devices were reviewed using standard search engine methods. PRISMA methods were used to evaluate and screen publications that included an evaluation of an effect on HF hospitalizations. All publications meeting the inclusion criteria were included, and the outcomes data were evaluated using standard meta-analysis methodology. Of 317 publications initially identified, five trials involving 1296 patients with chronic HF met the criteria used in this meta-analysis. Studies included prospective controlled designs, as well as observational studies with historical control. Heterogeneity testing failed to demonstrate instability of analysis due to differences between trials. When compiled, outcomes from these trials favoured remote haemodynamic monitoring with a significant 38% reduction in HF hospitalizations (hazard ratio 0.62, 95% confidence interval 0.50–0.78, \(P < 0.001\)).

**Conclusions**
Haemodynamic-guided HF management using permanently implanted sensors and frequent filling pressure evaluation is superior to traditional clinical management strategies in reducing long-term HF hospitalization risk in symptomatic patients.

**Keywords**
Haemodynamic monitoring • Heart failure • Hospitalizations • Meta-analysis

**Introduction**
Heart failure (HF) is a complex clinical syndrome with significant global public health consequences. Approximately 26 million people worldwide are affected by chronic HF.¹ Landmark drug and device therapies, shown to improve clinical outcomes in randomized controlled trials significantly, led to consensus from the medical community that neurohormonal blockade, implantable cardioverter-defibrillators (ICDs), CRT devices, mechanical circulatory support, and transplant should be considered and offered to appropriate patients with HF.² ³ Utilization of these interventions is the focus of quality initiatives in many geographic locales. Even with these therapeutic modalities, morbidity and mortality in HF remain a major burden.⁴–⁶ Particularly important to note is that HF hospitalizations are increasing worldwide generally corresponding to an ageing population.⁵–⁸ As the global population continues to age, HF will become even more prevalent. Accordingly, costs of caring for patients with HF are projected to double by 2030,⁸ with hospitalizations accounting for 80% of these costs.

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Several clinical strategies have been tested in randomized trials including care-matrix infrastructures to evaluate and monitor patients frequently, intense telemonitoring of signs of worsening symptoms or changes in home weight measurements, and remote monitoring of implantable device markers of congestion, such as intrathoracic impedance.\(^{7–11}\) In one trial, automatic remote monitoring of device-based diagnostics, such as arrhythmia incidence or loss of biventricular pacing, improved clinical outcomes in patients with reduced LVEF who also had previously implanted ICD or CRT devices.\(^{14}\) Although meta-analyses suggest that intense monitoring of weights and symptoms from the patients’ home may improve outcomes,\(^{15}\) large prospective randomized clinical trials fail to demonstrate an effect of monitoring these parameters on rehospitalizations.

Therefore, new remote management strategies are needed. In particular it is important to identify and focus especially on signals that provide enough insight into the pathophysiology of decompensated HF to prevent acute progression leading to hospitalizations. These signals should account for several components of the pathophysiology contributing to decompensation, including detection of exogenous volume accumulation and endogenous volume redistribution. Furthermore, remotely obtained signals must provide actionable data useful not only for early detection of decompensation, but also to guide therapy.\(^{16}\) One such strategy, haemodynamic-guided HF medical management using information from fully implantable sensors, has been tested in a variety of clinical trial settings with a variety of sensor technologies. The available evidence supporting implantable haemodynamic monitoring of HF patients led to a IIb(B) recommendation for use in the European Society of Cardiology (ESC) Heart Failure Guidelines for HF management.\(^{5}\) To evaluate this concept further, it is the goal of this meta-analysis to estimate a generalizable effect from all completed clinical trials testing whether haemodynamic-guided HF management, using implantable sensors, reduces HF hospitalizations.

**Methods**

**Literature review of heart failure management using implantable haemodynamic monitoring systems**

The purpose of this meta-analysis is to evaluate the effects of haemodynamic-guided HF management using implantable sensor technology on HF hospitalizations as reported in the literature. An extensive search of PubMed and the Cochrane Library was performed through to 28 April 2016 using the key words ‘haemodynamic monitoring’ AND ‘hospitalization’ AND ‘heart failure’ OR ‘left atrial pressure’ AND ‘heart failure’ AND ‘monitoring’ (see the Supplementary material online, Appendix S1 for search terms and results). In addition to literature searches, records from the US Food and Drug Administration (FDA) were reviewed to obtain specific information about clinical trials identified in the literature search. Three of the authors were involved in the leadership of all implantable haemodynamic monitoring trials (P.B.A., W.T.A., and R.C.B.) designed to determine an effect on HF hospitalizations and contributed to the literature review. The remaining authors provided statistical and meta-analysis expertise (G.G. and S.D.A.) and provided important interpretive input from HF monitoring trials to ensure a global modelling perspective (S.D.A.). For all publications screened and chosen for this meta-analysis, participant characteristics were analysed. Publications evaluating managing patients with HF with haemodynamic guidance using a permanently implantable device compared with patients managed using standard therapy strategies were chosen. Publications were required to evaluate the impact of haemodynamic-guided care on the rate of HF hospitalizations or equivalents. Included trials were required to evaluate HF hospitalizations as a component of the primary endpoint, including prospective, as well as observational designs. To avoid selection bias, all published trials were included in this analysis without regard to the authors’ contention concerning the trial’s empowerment to test the hypotheses, and results of the trials were based on published data. Abstracts or non-published observational data sets were not considered to be at a level of evidence high enough to be included in the analyses; however, source information published on the FDA website was accessed if detailed information was needed to evaluate an outcome further, but was not included in the published manuscript.

**Meta-analysis methods**

Data from this search were analysed using NCSS 10 (NCSS 2015), which uses the natural log (Ln) of the hazard ratios (HRs) that are transformed back to the original units using the exponential function. If a HR was not provided in the trial, one was calculated based on outcomes reported in the study, or obtained from public information published by the FDA. Both fixed and random effects models were used to calculate the average HR and 95% confidence interval (CI). The fixed effects model assumes that studies have a common true effect estimated by a weighted average of the individual study effects. The random effects model typically produces a wider CI than the fixed effects model. If both models produce similar results, this indicates that there is little to no evidence of heterogeneity. To ensure further that heterogeneity is not present, the effect-equality (heterogeneity) test\(^{17}\) was performed at a significance level of 0.10 to test the null hypothesis that all effects are equal (homogeneous) vs. the alternative that at least one effect was different (heterogeneous). Finally, the \(I^2\) statistic was also computed which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. \(I^2\) values <40% are generally used to indicate a lack of heterogeneity.\(^{18–20}\) In observational studies, subjects served as their own controls so that unmeasured time-invariant factors are differentiated out.\(^{19}\) In advanced progressive disease states such as symptomatic HF, patient outcomes are expected to worsen over time. Thus, these study designs may be conservative and an appropriate choice for testing new haemodynamic monitoring technology. Further potential confounding and bias from the smaller observational studies were minimized by weighting techniques used in the meta-analysis process.

A forest plot of the study results was produced from these methods comparing outcomes with the line of unity. To control further for heterogeneity, a forest plot was also produced using HRs derived only from randomized, prospective clinical trials which included NYHA class II–IV patients.

**Results**

**Search results and description of included trials**

A total of 317 articles were identified using the search terms outlined in the Methods and as shown in the PRISMA flow
chart illustrated in Figure 1 (see Supplementary material online, Appendix S2 for details). Five publications were found reporting unique results from trials evaluating HF management guided by implantable haemodynamic monitoring devices and met the inclusion criteria of this meta-analysis. Characteristics of the five trials are summarized in Table 1 and detailed in the Supplementary material online, Appendix S3. Demographic and subject characteristics from each trial are outlined in Table 2. All trials used implantable technology, albeit different devices and sites of monitoring, to provide information about changes in medical therapies for patients assigned to haemodynamic-guided care. None of the technologies inherently provided ‘treatment’, but instead the trials considered haemodynamic guidance as a ‘treatment strategy’, thus patients were assigned to a ‘treatment’ or ‘control’ group.

The risk of potential bias of individual studies was assessed at the study-type level. First, the random effects model was used to provide pooled results weighted according to study. Also, there were two prospective observational studies reporting similar results (each HR <0.5) and three randomized controlled trials. The pooled effects were generated excluding the two observational studies and the pooled HR was 0.68 (95% CI 0.55–0.85). Thus the potential bias from the two observational studies did not alter the conclusions.

Detailed design descriptions of trials included in the meta-analysis

The five trials in this meta-analysis were the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association (NYHA) Class III Heart Failure Patients (CHAMPION) trial (ClinicalTrials.gov #NCT00531661), the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) Trial, the Chronicle Feasibility Study, the Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients with Chronic Heart Failure (REDUCEhf) Trial, and the Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Trial. Characteristics of the five trials included in this meta-analysis are listed in Table 1 and a detailed description of the trial designs is included in the Supplementary material online, Appendix S3. All prospective trials required patients to have a previous hospitalization and some level of residual HF symptoms (NYHA class II–IV) despite maximal therapies as detailed in Table 1.

Meta-analysis results

Meta-analysis using outcomes from these trials found a statistically significant 38% reduction (HR 0.62, 95% CI 0.50–0.78,
**Table 1** Characteristics of the five studies identified using implantable haemodynamic monitoring technology to guide heart failure management

| Study details | Chronicle (n = 32) | HOMEOUSTASIS (n = 40) | CHAMPION (n = 550) | COMPASS-HF (n = 274) | REDUCEHF (n = 400) |
|---------------|-------------------|-----------------------|--------------------|----------------------|--------------------|
| **Years of study** | Published 2003 | Prospective, observational, historic control | 2005–2008 | Prospective, observational, open label | 2007–2009 | Prospective, single-blinded, randomized control |
| **Device type** | Implanted RV | Implanted LA pressure sensor with RF uplink | Wireless implanted MEMS-based PA pressure sensor | Implanted RV intracardiac continuous haemodynamic monitor | Implanted ICD with RV intracardiac continuous haemodynamic sensor |
| **NYHA class** | II–III | III | III | III–IV | II–III |
| **Previous hospitalization requirement** | None | None | At least 1 HFH in the previous 12 months | At least 1 HFH in the previous 6 months | At least 1 HFH in the previous 12 months |
| **Treatment recommendations** | None | Target pressures with medication change suggestions | Target pressures with medication change suggestions | 'Optivolaemic' ranges without medication change recommendation | 'Optivolaemic' ranges without medication change recommendation |
| **Average follow-up** | 17 months | 25 months | 18 months | 6 months | 12 months |
| **Endpoint** | HFH | Death or HFH | HFH | HFH | HFH |

Total n = 1296.
HFE, heart failure event (consisted of HFH, emergency department visit, or urgent clinic visits); HFH, heart failure hospitalization; ICD, implantable cardioverter defibrillator; LA, left atrial; PA, pulmonary artery; RV, right ventricular.

*Annualized all-cause deaths and HFH were compared with HFH rate in the previous year of 1.4 HFH events/patient-year.
†Time to first HFH.

**Table 2** Demographic and baseline characteristics of subjects included in the five trials evaluated in this meta-analysis

| Patient characteristics | Chronicle (n = 32) | HOMEOUSTASIS (n = 40) | CHAMPION (n = 550) | COMPASS-HF (n = 274) | REDUCEHF (n = 400) |
|-------------------------|-------------------|-----------------------|--------------------|----------------------|--------------------|
| **Age (years ± SD)** | 59 ± 10 | 66 ± 10 | 61 ± 13 | 58 ± 14 | 55 ± 15 |
| **Gender (% male)** | 38 | 78 | 73 | 65 | 69 |
| **Race (% Caucasian)** | NR | NR | 73 | 77 | 57 |
| **LVEF (% mean ± SD)** | 29 ± 11 | 32 ± 12 | 78 < 40 | 74 < 50 | 23 ± 8 |
| **NYHA (I, II, III, IV)** | (3, 4, 53, 0) | 3.0^a | (0, 0, 100, 0) | (0, 0, 85, 15) | (0, 49, 51, 0) |
| **Aetiology of HF (% ischaemic)** | 59 | 73^b | 60 | 46 | 45 |

HF, heart failure; NR, not reported.
^aMedian (range) NYHA class = III (II–III).
^bDefined as a history of myocardial infarction.
^c<0.001 in HF events comparing haemodynamic-guided HF management with care provided in organized HF disease management programmes using random effects modelling (Figure 2; Table 3). Modelling using fixed effects methodology demonstrated similar results, with a 37% reduction in HF hospitalizations (HR 0.63, 95% CI 0.54–0.73, P < 0.0001). Lack of heterogeneity was confirmed by the similarity between the fixed and random effects mode as well as the non-significant Cochran’s Q heterogeneity test result (P = 0.222). Also, the R^2 statistic of 29.9% was <40%, indicating that the percentage of variability in the effect estimates, due to heterogeneity, is likely to be unimportant.
Figure 2 Findings from meta-analysis of five trials evaluating the impact of haemodynamic-guided heart failure management in patients with symptomatic heart failure. The average point-estimate of impact on preventing hospitalizations is 38% [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.50–0.78, \( P < 0.001 \)] using a random effects model and 37% (HR 0.63, 95% CI 0.54–0.73, \( P < 0.001 \)) using a fixed effects model.

COMPASS_FEAS, Chronicle Feasibility Study; HOMEOSTASIS; CHAMPION; COMPASS-HF; REDUCEhf.

The ‘Average’ line presents the combined estimates of the studies using both random and fixed effects models.

Effect-equality (heterogeneity) test: Cochran’s \( Q = 5.7085, \text{df} = 4, P = 0.2220 \) (not significant if \( P < 0.10 \)).

\( I^2 \) index of heterogeneity = 29.9% (values <40% indicate no evidence of heterogeneity).

HR, hazard ratio; LCL, lower confidence limit; SE, standard error; UCL, upper confidence limit.

To reduce further the risks of heterogeneity, the meta-analysis was limited to only prospective randomized trials demonstrating a 32% reduction in HF hospitalizations (HR 0.68, 95% CI 0.55–0.85) and included results from 1224 of the 1296 subjects studied (Figure 3; Table 4).

Discussion

This meta-analysis includes the results from all trials evaluating haemodynamic-guided HF management directed by implantable devices and demonstrates that HF hospitalization rates are 38% lower when patients are treated using haemodynamic guidance. The trials include devices that measure left atrial pressure, pulmonary artery pressure, and right ventricular pressures with estimates of pulmonary artery pressures. Although the point estimates of effect in reducing HF hospitalizations are similar regardless of the site of pressure measurement, only one trial was able to evaluate left atrial pressure. Regardless, these trials support the hypothesis that filling pressures provide meaningful insight into the pathophysiology of decompensating HF. In one of the trials (CHAMPION), pressure information led to specific alterations in medical management, primarily by increasing or decreasing diuretics...
in response to changes in pressures, adding vasodilator therapy for resistant pressures, and also allowed further up-titration of neurohormonal antagonists. Only the CHAMPION trial and the HOMEOSTASIS study included pressure-based treatment recommendations in the study protocols. Specific medication changes are not available from the other trials.

Overall, the findings of this meta-analysis are consistent with observations from the COMPASS-HF trial demonstrating a direct relationship between elevated pressures and hospitalization risks. Lowering pressures with medical management in that trial was directly associated with lower hospitalization risk. Outcomes using this approach across several trials suggest that filling pressures complete the requirements of an ideal remotely obtained signal, suggested by Desai and Stevenson, by accurately describing the underlying HF pathophysiology, providing ‘actionable’ information and a means to follow up the results of a change in medical management. At a time in which HF is becoming more prevalent and hospitalizations more burdensome, these findings are encouraging, especially in light of the failure of multiple other strategies to reduce hospitalizations by remotely managing HF patients.

### Patient selection

Whereas a combination of patients with NYHA class II–IV was studied in the trials reviewed, the largest common cohort was previously hospitalized patients who persistently had congestive symptoms limiting activity (NYHA class III). Patients with NYHA class II symptoms after hospitalization have very low subsequent risk for rehospitalization, while those with refractory NYHA class IV symptoms appear to be too sick for haemodynamic monitoring to reduce hospital needs. Further study in these groups may find benefit of haemodynamic monitoring, but currently clinical trial evidence suggests that remote haemodynamic-guided HF care should not be considered for all patients with HF.

In addition to patient selection, each trial reviewed required an established infrastructure to review regularly transmitted pressures with a mechanism to act on the information. None of the haemodynamic monitors tested in clinical trials delivers therapy on their own, but they merely provide information. Results similar to the clinical trials included in this analysis would not be expected if the remotely obtained information is not actively used to manage patients. Additionally, the frequency of review was very consistent across trial protocols and instructed investigators to evaluate pressures weekly, even though information was remotely uploaded to Internet-based information systems daily. The daily uploaded information provided a trend analysis as the basis for medication change based on the observations that filling pressure changes can be detected weeks before clinical symptoms develop.

### Limitations

Although meta-analyses provide an opportunity to pool data from similarly designed clinical trials and simulate possible outcomes from larger sample sizes, differences between groups and statistical evaluations between trials may confound the results of meta-analyses. The current analysis includes findings from

### Table 4 Statistical summary of results from the meta-analysis methods used to evaluate prospective randomized controlled trials only

| Study                | Natural log (Ln) of HR | Ln HR | SE  | 95% LCL     | 95% UCL     | HR      | 95% LCL  | 95% UCL  | % Random effects weight | % Fixed effects weight |
|----------------------|------------------------|-------|-----|-------------|-------------|---------|----------|----------|------------------------|------------------------|
| CHAMPION (n = 550)   | −0.462                 | 0.100 | −0.658 | −0.266     | 0.630       | 0.518   | 0.766    | 62.3     | 72.9                   |
| COMPASS-HF (n = 274) | −0.446                 | 0.211 | −0.860 | −0.032     | 0.640       | 0.423   | 0.968    | 14.0     | 16.4                   |
| REDUCE-HF (n = 400)  | −0.010                 | 0.260 | −0.520 | 0.500      | 0.990       | 0.595   | 1.648    | 9.2      | 10.8                   |
| Average—random effects | −0.385              | 0.114 | −0.607 | −0.162     | 0.681       | 0.545   | 0.850    | 100.0    | 100.0                  |
| Average—fixed effects | −0.411               | 0.085 | −0.578 | −0.243     | 0.663       | 0.561   | 0.784    | 100.0    | 100.0                  |

The ‘Average’ line presents the combined estimates of the studies using both random and fixed effects models.

Effect-equality (heterogeneity) test: Cochran’s Q = 2.666, df = 2, P = 0.2636 (not significant if P < 0.10).

P index of heterogeneity = 25.0% (values <40% indicate no evidence of heterogeneity).

HR, hazard ratio; LCL, lower confidence limit; SE, standard error; UCL, upper confidence limit.

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prospective randomized single-blinded clinical trials coupled with observational studies with smaller numbers. Point estimates in the smaller trials may be overstated due to the number of patients studied and lower level statistical meaning, as shown by the larger CIs seen in the smaller trials. Smaller numbers of patients studied and the availability of primary results from only five trials may lead to inaccurate estimation of effect. Although this meta-analysis is limited by the small number of prospective clinical trials, the results are encouraging and further support ESC-HF guideline recommendations. Importantly, new prospective randomized clinical trials further testing the hypothesis that haemodynamic-guided HF management is superior to reliance on traditional monitoring tools are needed.

Conclusions

This meta-analysis demonstrates that remote HF management based on measurement of cardiac filling pressures using an implanted pressure sensor is effective in preventing decompensation and reducing HF hospitalizations, and supports the recommendations outlined in the ESC-HF guidelines. Specifically, the totality of available evidence suggests that this approach is particularly useful in patients who remain symptomatic following a previous hospitalization despite the application of tolerated guideline-directed medical therapies, regardless of their underlying LVEF.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. PRISMA 2009 checklist.
Appendix S2. Unique references found on PubMed using PRISMA methods.
Appendix S3. Description of individual trials included in the meta-analysis.

Conflict of interest: P.B.A.: Co-PI CHAMPION Trial, PI REDUCE-HF Trial, PI Chronic feasibility trial, Steering Committee HOMEOSTASIS, Steering Committee COMPASS-HF. Currently an employee of St. Jude Medical and an Adjunct Associate Professor of Physiology at the University of Oklahoma Health Sciences Center in Oklahoma City, OK, USA; G.G.: employee of St. Jude Medical.

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