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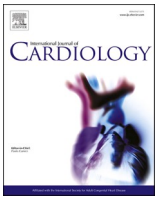

Heart failure management guided by remote multiparameter monitoring: A meta-analysis

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ABSTRACT

Background: Several implant-based remote monitoring strategies are currently tested to optimize heart failure (HF) management by anticipating clinical decompensation and preventing hospitalization. Among these solutions, the modern implantable cardioverter-defibrillator and cardiac resynchronization therapy devices have been equipped with sensors allowing continuous monitoring of multiple preclinical markers of worsening HF, including factors of autonomic adaptation, patient activity, and intrathoracic impedance.
Objectives: We aimed to assess whether implant-based multiparameter remote monitoring strategy for guided HF management improves clinical outcomes when compared to standard clinical care.
Methods: A systematic literature research for randomized controlled trials (RCTs) comparing multiparameter-guided HF management versus standard of care was performed on PubMed, Embase, and CENTRAL databases. Incidence rate ratios (IRRs) and associated 95% confidence intervals (CIs) were calculated using the Poisson regression model with random study effects. The primary outcome was a composite of all-cause death and HF hospitalization events, whereas secondary endpoints included the individual components of the primary outcome.
Results: Our meta-analysis included 6 RCTs, amounting to a total of 4869 patients with an average follow-up time of 18 months. Compared with standard clinical management, the multiparameter-guided strategy reduced the risk of the primary composite outcome (IRR 0.83, 95%CI 0.71–0.99), driven by statistically significant effect on both HF hospitalization events (IRR 0.75, 95%CI 0.61–0.93) and all-cause death (IRR 0.80, 95%CI 0.66–0.96).
Conclusion: Implant-based multiparameter remote monitoring strategy for guided HF management is associated with significant benefit on clinical outcomes compared to standard clinical care, providing a benefit on both hospitalization events and all-cause death.

Abbreviations: CI, Confidence interval; CIEDs, Cardiac implantable electronic devices; CRT, Cardiac resynchronization therapy; ESC, European Society of Cardiology; HF, Heart failure; HRV, Heart rate variability; ICD, Implantable cardioverter-defibrillator; IRR, Incidence rate ratio; NYHA, New York Heart Association; RCT, Randomized clinical trial.

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1. Introduction

Heart failure (HF) represents a major challenge for cardiologists of our time. The rising burden of chronic HF, with spreading numbers of related adverse events across Europe (1,2) and US (3,4), demands for advancing technologies to improve patient outcomes and mitigate the social, clinical, and economic load on healthcare systems. The hospitalization rate of patients with HF remains excessively high while recurrent HF decompensation events impact negatively on morbidity and mortality. (5,6) Several telemedical programs have been tested to provide continuous remote monitoring of HF patients, thus enabling early detection of impending decompensation and timely intervention to prevent hospitalization. Non-invasive telemonitoring failed to show a significant effect on clinical outcomes due to the delayed onset of clinical signs and symptoms of worsening HF (7–10). Conversely, randomized clinical trials (RCTs) testing remote monitoring strategies based on implanted devices provided promising results (11,12), although with different impact according to parameters monitored (13). To maximize the technological advancement, the modern cardiac implantable electronic devices (CIEDs) have been equipped with sensors allowing an automatic daily remote monitoring of multiple parameters, including preclinical markers of worsening HF such as parameters related to autonomic adaptation (14–16), reduced patient activity (17), and pulmonary fluid accumulation (18). Operative algorithms were created to shift from remote monitoring to systematic remote management, thus obtaining a concrete therapeutic effect. The application of such technologies in implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices enabled the development of a multiparameter monitoring strategy, possibly granting a prompt and targeted therapeutic response to subclinical HF deterioration. The sustainability of such approach has already been proven in previous trials and meta-analyses (19–22). Yet, conclusive evidence of benefit on patient outcomes is lacking (21,22). On this background, we performed a systematic review and meta-analysis of RCTs comparing the effects on clinical outcomes of implant-based multiparameter remote monitoring strategy to guide HF management versus standard of care.

2. Methods

The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for conducting this systematic review and meta-analysis (23). The protocol was registered within the international prospective register of systematic reviews (PROSPERO, CRD42022308167).

2.1. Search strategy and inclusion criteria

On Jan 14, 2022, we performed a systematic and comprehensive literature research using PubMed, Embase, and Cochrane Central Register of Controlled Trials databases. In addition, we made backward snowballing research (i.e., a review of references from identified articles). A combination of the following search terms was used: “monitoring”, “telemedicine”, “impedance”, “implantable cardioverter defibrillator”, “cardiac resynchronization therapy”, and “heart failure”. The full search strategy is available in Supplementary material, Table S2. Two investigators systematically and independently screened all records retrieved from the research. Eligibility was assessed according to titles and abstracts. Articles potentially suitable were assessed for inclusion by inspecting full-text and supplementary material. We included RCTs that enrolled patients with HF, compared implant-based multiparameter remote monitoring strategy to guide HF management versus standard of care and assessed clinical outcomes. Studies testing telemonitoring strategies only as a substitute for in-clinic follow-up, not reporting clinical outcomes, or with overlapping populations were excluded. We have applied no restrictions for study language, follow-up duration, and publication date.

2.2. Data extraction and quality assessment

Study design and features, patients’ characteristics, and outcomes were extracted independently by two investigators using a standardized data worksheet. When multiple studies were reported from the same cohort of subjects, the one with the longest follow-up was included in the analysis. Conflicts were resolved by collegial discussion.

The risk of bias assessment was independently made by two investigators according to the Cochrane Collaboration risk-of-bias tool (RoB2), composed of five domains: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported result. (24)

2.3. Outcomes definition

The primary outcome was a composite of all-cause death and hospitalizations for HF (including recurrent events). Secondary outcomes included the individual components of the primary outcome (i.e., all-cause death and hospitalizations for HF). For the assessment of the primary outcome, two studies did not report the number of HF hospitalizations and the outcome of unplanned hospitalization for cardiovascular reasons was included (25,26). Endpoint definitions of each study are reported in Supplementary material, Table S4.

2.4. Statistical analysis

A patient-years approach was adopted to address different follow-up times and recurrent events. When the number of patient-years was not clearly reported, it was arithmetically calculated by multiplying the number of patients by the years of follow-up (for each arm, if available). Incidence rate ratios (IRRs) and the associated 95% confidence intervals (CIs) were calculated using the mixed-effects Poisson regression model with random study effects. The heterogeneity between studies was evaluated using Cochran’s Q test, while Higgins and Thompson I^2 was computed to estimate the proportion of total variability due to between-study heterogeneity. The potential presence of publication bias was assessed by visual inspection of funnel plots and using the Egger test.

A prespecified sensitivity analysis using the leave-one-out approach was performed removing all studies one at a time to investigate the influence of each study on the overall effect-size estimate. Furthermore, a post-hoc sensitivity analyses was performed excluding two studies enrolling a small proportion of patients without HF (26,27).

Several univariable meta-regression analyses were performed to assess the presence of a relation between some covariates (age, left ventricular ejection fraction, proportion of patients with atrial fibrillation, proportion of patients with heart failure of ischemic cause, proportion of patients in different NYHA functional classes, and proportion of patients treated with different drugs) and treatment effect for all outcomes. A two-sided *p*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R version 4.1.2 (The R Foundation, 2021) “meta” package.

3. Results

A total of 13,496 articles were initially screened and six RCTs were identified and included in this study (Supplementary material, Table S3). A total of 4869 patients randomly allocated to multiparameter-guided management ($n = 2674$) or standard care ($n = 2195$) were included in the analysis. The average follow-up duration was 18 months. The device used was ICD or CRT in all trials (Table) and the remote monitoring platform was Home Monitoring (Biotronik) in four out of six trials (12,26–28) (Supplementary material, Table S5). On the other hand, the other two trials (25,29) included different remote monitoring platforms in the multiparameter-guided management arm: MyCareLink (Medtronic), Merlin.net (St. Jude Medical), Home

Monitoring (Biotronik), and Latitude (Boston Scientific) (Supplementary material, Table S5). The key features of included trials and patient baseline characteristics are summarized in the Table and the Supplementary material, Table S5 and Table S6. The risk-of-bias assessment identified three studies at low risk of bias and three studies with some concerns (Supplementary material, Fig. S1).

Compared with standard therapy, multiparameter-guided HF management significantly reduced the risk of the primary composite outcome of all-cause death and hospitalizations for HF (IRR 0.83, 95% CI 0.71–0.99, $p = 0.033$, $I^2 = 40\%$; Fig. 1). This result was driven by a reduction in the risks of both all-cause death (IRR 0.80, 95% CI 0.66–0.96, $p = 0.017$, $I^2 = 14\%$; Figure) and hospitalizations for HF (IRR 0.75, 95% CI 0.61–0.93, $p = 0.007$, $I^2 = 0\%$; Figure). (See Table 1.)

At leave-one-out sensitivity analyses (Supplementary material, Fig. S2), no trial showed a significant influence on the pooled estimate for the outcome of HF hospitalizations. On the other hand, the exclusion of IN-TIME (30) leads to slightly non-significant results for the outcome of all-cause death, and the exclusion of four trials (26,28–30) leads to slightly non-significant results for the primary composite outcome, albeit without critically affecting the point estimate. The analyses

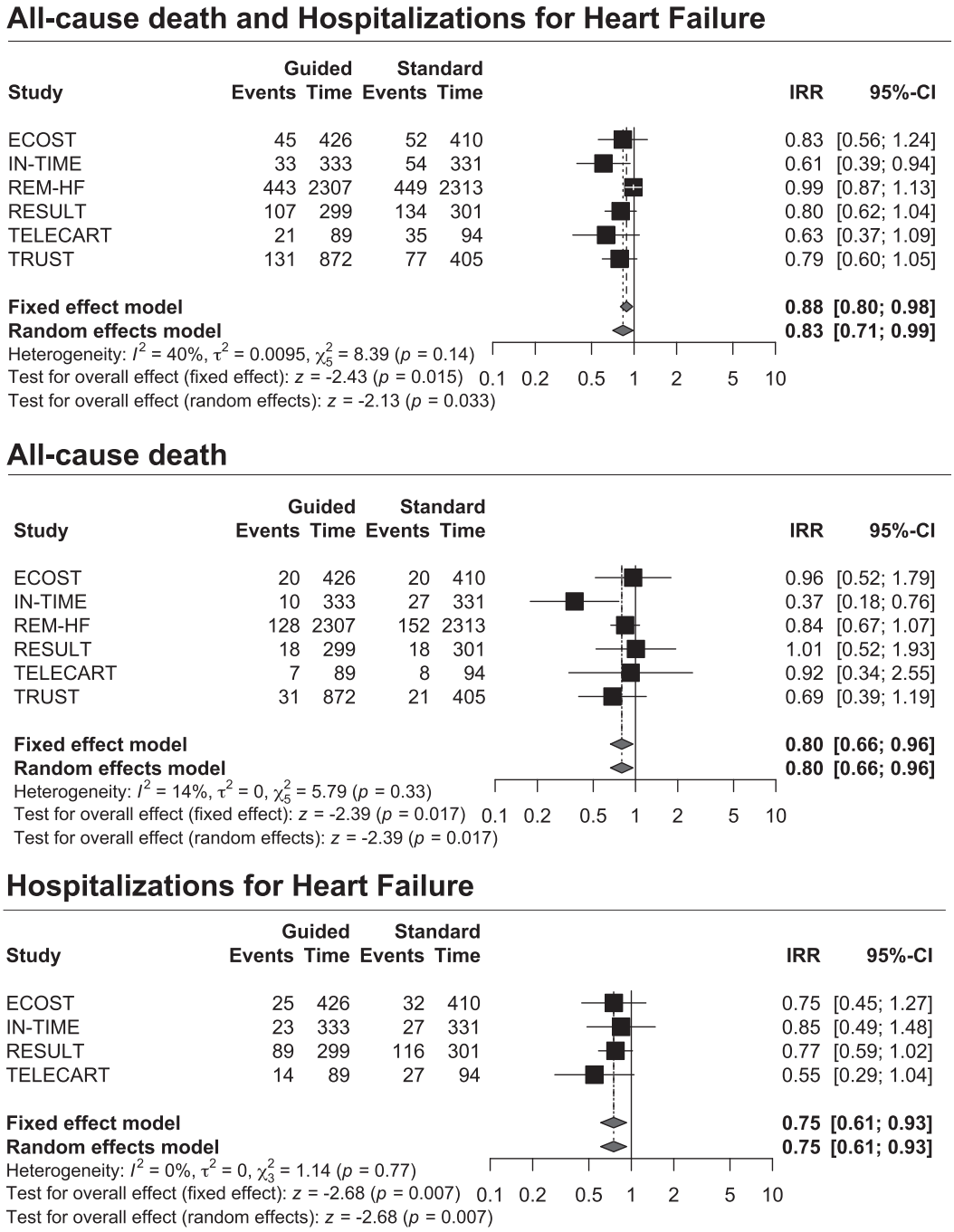

Fig. 1. Multiparameter-guided management versus standard therapy for the primary and secondary outcome. CI, confidence interval; IRR, incidence rate ratio; Time, patient-years.

Table 1
Title: Key features of randomized controlled trials included in the meta-analysis.

	Year	Device	Number of patients			Major parameters guiding management		Follow-up
			Overall	Guided management	Control	Guided management	Control	
ECOST	2013	ICD	433	221	212	Atrial or ventricular tachyarrhythmias, patient activity	Usual care	24 months
IN-TIME	2014	ICD/CRT	664	333	331	Atrial or ventricular tachyarrhythmias, patient activity	Usual care	12 months
REM-HF	2017	ICD/CRT	1650	824	826	Intrathoracic impedance, atrial or ventricular tachyarrhythmias, patient activity	Usual care	34 months
RESULT	2020	ICD/CRT	600	299	301	Atrial or ventricular tachyarrhythmias, patient activity	Usual care	12 months
TELECART	2016	CRT	183	89	94	Atrial or ventricular tachyarrhythmias, patient activity	Usual care	12 months
TRUST	2010	ICD	1339	908	431	Atrial or ventricular tachyarrhythmias, patient activity	Usual care	12 months

Abbreviations: CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; ICHM = implantable continuous haemodynamic monitor.

excluding trials enrolling a small proportion of patients without HF (26,27) (Supplementary material, Fig. S3) showed consistent findings with the main analyses, except for a marginal non-significant reduction in the risk of the primary composite outcome (IRR 0.83, 95% CI 0.65–1.04, $p = 0.110$, $I^2 = 60\%$) with a strategy of multiparameter-guided management compared with standard therapy.

Meta-regression analyses showed no significant relation between all covariates (age, left ventricular ejection fraction, proportion of patients with atrial fibrillation, proportion of patients with heart failure of ischemic cause, proportion of patients in different NYHA functional classes, and proportion of patients treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β blockers, mineralocorticoid receptor antagonists, and diuretic) and treatment effect for all outcomes (Supplementary material, Table S8), except for a marginal direct relation of the primary composite outcome with atrial fibrillation and NYHA functional class II. Funnel plots and Egger tests suggested no evidence of publication bias or small study effect (Supplementary material, Fig. S4), except for a potential publication bias for the primary composite outcome.

4. Discussion

This meta-analysis of six RCTs involving 4869 patients shows that, compared with standard therapy, guided HF management according to implant-based multiparameter monitoring strategy is associated with a lower risk of the composite endpoint of all-cause death and HF hospitalization events, driven by a benefit in both individual components (Central Illustration).

Despite the better knowledge and the improvement in diagnostic and therapeutic tools, a substantial proportion of HF patients remains undermanaged, and under-treated and, consequently, have a poor prognosis (31–33). In this context, the evidence for a role of implantable devices in detecting preclinical markers of worsening HF and improving clinical outcomes is growing (11,30,34,35). However, since a clear benefit was not always confirmed in largest RCTs (25,36,37), current guidelines do not strongly recommend remote monitoring strategies to manage heart failure patients (32,38).

A recent meta-analysis focusing on congestion-guided HF management demonstrated that HF management according to intracardiac or pulmonary artery pressures values could significantly reduce HF hospitalizations (13). These findings reflect the well-established pathophysiological progression from chronic compensated to acute decompensated HF, in which the earliest hallmark is an increase in ventricular filling pressures (39). Conversely, RCTs included in this meta-analysis tested a remote monitoring strategy for guided HF management based on a set of multiple preclinical markers of worsening HF, including factors of autonomic adaptation (i.e., the heart rate variability [HRV], the onset of atrial or ventricular arrhythmias, and the rate of biventricular pacing) (14–16), patient activity (17), and intrathoracic impedance (18). Since the pathophysiology underlying HF is characterized by sympathetic activation (40,41) and parasympathetic withdrawal triggered by decreased cardiac output, autonomic adaptation is considered a hallmark of HF status (42). The HRV may be considered a marker of "autonomic response". It is lower in HF patients with high hospitalization risk and it decreases with progressive HF worsening (14). Implantable devices may detect also other markers of autonomic adaptation that simultaneously act as exacerbating factors, such as the onset of atrial or ventricular arrhythmias and the reduced rate of biventricular pacing (15,16). Furthermore, daily physical activity is another useful worsening marker since its reduction is known to be a predictor of decompensation (17). Finally, intrathoracic impedance is a marker of pulmonary fluid accumulation and decreases with progressive pulmonary congestion (17,18,35,43). However, it represents a late sign of HF decompensation and its use as a unique monitoring parameter in impedance-guided management strategy did not appear to impact the risks of death and HF hospitalization (13). The alteration of all these parameters typically follows the increase in cardiac filling pressure in the progression of worsening HF (44), but the opportunity to rely on multiple parameters may eventually enable a quick detection of degenerating conditions far before the occurring of symptomatic congestion, thus enabling a prompt therapeutic response aimed at preventing hospitalization events and urgent visits.

In contrast to haemodynamic-guided management strategy (13), multiparameter-guided strategy has been shown to reduce not only HF hospitalizations but also all-cause mortality during a 18-month follow-up. In this context, a strategy of multiparameter monitoring as a tool for continuous optimization of care showed high effectiveness in directing HF management, probably because concordant changes in a pool of parameters are more effective in alerting physicians of worsening decompensation, while a change in a single parameter like onset of atrial fibrillation or reduced percentage of biventricular pacing could be useful to trigger a specific therapeutic response (45,46).

In addition to preventing HF exacerbation, a multiparameter-guided strategy might aim to identify different patient subsets, reflecting different disease phenotypes, labelled according to the dominant mechanism of disease (e.g., hemodynamic, autonomic, arrhythmic, congestive etc.), or to the combination of them. Hopefully, this approach might represent an additive tool to personalize HF management (47,48).

The relevance of our systematic review lies on the evidence that all but one (11) of the previous RCTs on this topic, when taken individually, failed to provide a statistically significant result. The absence of strong recommendation in current HF guidelines descends from the fact that previous studies lacked statistical power to clearly assess a hard efficacy endpoint. This comprehensive meta-analysis overcame these limitations and succeeded in showing a statistically significant effect of multiparameter-guided HF management on all-cause death and

hospitalizations.

Previous meta-analyses on this topic were conflicting since pooled RCTs testing heterogeneous telemonitoring systems, including approaches aimed at substituting in-clinic follow-up (21,22,49–52). Conversely, our meta-analysis focused on the challenging task of fully implementing ICD/CRT-based remote monitoring strategy to guide HF management with a targeted therapeutic response according to changes in preclinical markers of worsening HF.

Device telemonitoring requires accurate tools, both to avoid missing detection of worsening heart failure and to minimize false alerts. As technology innovation progresses, it seems reasonable to infer that the efficacy of such strategies may only increase. Of note, as technical advancement may affect the assessment of multiple parameters, the final improvement could be exponential.

As recently highlighted even by the ESC guidelines (32), self-care is emerging as a cornerstone in the long-term management of chronic HF patients, stressing the relevance of patient education on treatment adherence, lifestyle changes, symptoms monitoring, and adequate response to possible deterioration. The data presented in this original manuscript might reinforce this concept, further strengthening the alliance between patients and healthcare professionals sharing the common goal to ameliorate person-centred outcomes such as better quality of life and lower mortality and readmission rates.

The effectiveness of device-based remote monitoring could adequately face the growing economic burden of HF management, as most of the costs are incurred from in-hospital treatment of clinical decompensations (19). To this end, previous data showed that remote monitoring of HF patients by implantable device is cost saving, granting a reduction in healthcare resource utilization, mostly driven by a reduction in in-hospital visits and HF hospitalizations (19–21), thus supporting the importance of shifting care from hospital to home. Nevertheless, costs were not always detailed in previous trials. Therefore, future studies prospectively collecting economic data are needed, aiming to final validation of the cost-effectiveness of a device-based multiparameter-guided strategy for HF patients.

4.1. Limitations

Our study has several limitations. First, the literature research was conducted using three databases (PubMed, Embase, Cochrane). Second, the lack of patient-level data does not allow to assess potential treatment modifiers. Third, the included RCTs used platforms with different technical aspects and not all trials fully reported which alerts triggered a therapeutic response. However, four of the six trials used the same platform, providing results legitimacy (26–28,30). Fourth, one trial reported an endpoint of the first hospitalization instead of recurrent hospitalizations. Yet, a sensitivity analysis using leave-one-out approach showed that results remained consistent with the main analysis when this trial was excluded. Fifth, two studies enrolled a small proportion of patients without HF. In this regard, a sensitivity analysis excluding these two RCTs showed findings consistent with the main analysis. Last, the use of the patient-years approach may introduce a bias due to partially reported arm-specific follow-up times, but the inclusion of only RCTs and the use of the Poisson regression model contributed to bias mitigation and results validation (53).

5. Conclusion

Implant-based remote monitoring strategies for multiparameter-guided HF management is associated with significant benefit on clinical outcomes compared to standard clinical care. Multiparameter-guided strategy grants a reduction of the composite endpoint of all-cause death and HF hospitalizations, driven by a benefit in both individual components. Further studies are needed to test the cost-effectiveness of implant-based remote monitoring in guiding the management of HF patients, potentially legitimizing a wide application of such strategy.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131163.

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