Device-based remote monitoring strategies for congestion-guided management of patients with heart failure: a systematic review and meta-analysis

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ABSTRACT

Aims: Preclinical congestion markers of worsening heart failure (HF) can be monitored by devices and may support the management of patients with HF. We aimed to assess whether congestion-guided HF management according to device-based remote monitoring strategies is more effective than standard therapy.

Methods and results: A comprehensive literature research for randomized controlled trials (RCTs) comparing device-based remote monitoring strategies for congestion-guided HF management versus standard therapy 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 hospitalizations. Secondary endpoints included the individual components of the primary outcome. A total of 4347 patients from 8 RCTs were included. Findings varied according to the type of parameters monitored. Compared with standard therapy, haemodynamic-guided strategy (4 trials, 2224 patients, 12-month follow-up) reduced the risk of the primary composite outcome (IRR 0.79, 95% CI 0.70-0.89) and HF hospitalizations (IRR 0.76, 95% CI 0.67-0.86), without a significant impact on all-cause death (IRR 0.93, 95% CI 0.72-1.21). In contrast, impedance-guided strategy (4 trials, 2123 patients, 19-month follow-up) did not provide significant benefits.

Conclusion: Haemodynamic-guided HF management is associated with better clinical outcomes as compared to standard clinical care.

KEYWORDS

Heart failure; Guided management; Remote monitoring; Telemonitoring; Hospitalization; Death.

ABBREVIATIONS

CI, Confidence interval;

HF, Heart failure;

IRR, Incidence rate ratio;

RCT, Randomized controlled trial.

INTRODUCTION

Heart failure (HF) is a growing public health and economic problem, affecting almost 64 million people worldwide.[1] Despite the recent advances in the therapeutic field with more frequent use of effective drug and device therapies, the natural history of patients with HF is characterized by poor quality of life, recurrent events of hospitalization, and a high rate of morbidity and mortality.[2,3] The hospitalization rate due to fluid overload and worsening HF remains high, affecting patients' long-term prognosis and burdening healthcare systems.[4] Therefore, to improve clinical outcomes and reduce healthcare costs, a wide range of invasive and non-invasive monitoring strategies aimed at preventing HF decompensation have been developed.[5] Firstly, several randomized controlled trials (RCTs) tested the hypothesis that careful monitoring of signs and symptoms of clinical deterioration (eg, dyspnea, weight gain, or peripheral edema) through non-invasive telemonitoring systems could lead to early medical management avoiding hospitalization.[6] However, these strategies have failed in their attempt since clinical parameters of fluid accumulation are delayed and unreliable as early signs of decompensation.[6–8] Later, the use of invasive devices able to automatically monitor physiological data allowed to continuously check preclinical markers of worsening HF, including congestion parameters such as increased intracardiac or pulmonary artery pressures and pulmonary fluid accumulation.[9,10] Remote monitoring strategies of these parameters to allow a prompt and targeted therapeutic response have been tested in various RCTs, often underpowered, which have led to conflicting results.[11–14]

Previous meta-analyses did not provide unequivocal results since they were selectively performed on a single guided management strategy[15,16], included studies testing telemonitoring systems as a

substitute for in-clinic follow-up, or assessed heterogeneous outcomes or heterogeneous strategies in the same subgroup[17–19], leading to questionable results. Therefore, to provide a comprehensive and updated evidence, we did a systematic review and meta-analysis of RCTs comparing device-based remote monitoring strategies to guide the management through congestion markers versus standard care in patients with HF.

METHODS

This systematic review and meta-analysis was carried out in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The protocol was registered within the international prospective register of systematic reviews (PROSPERO, CRD42022308167).

Search strategy and selection criteria

On Jan 14, 2022, we did 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., review of references from identified articles). A combination of the following search terms was used: “monitoring”, “telemedicine”, “haemodynamic”, “impedance”, “implantable cardioverter defibrillator”, “cardiac resynchronization therapy”, “heart failure”. The full search strategy is available in Supplementary material online, Table S2. Two investigators (A.Z. and G.P.) 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 inspecting full-text, supplementary material, and online appendices. We included all RCTs comparing a strategy of guided management according to device-based remotely monitored markers of congestion with standard therapy in patients with HF. 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.

For the purposes of this analysis, the included trials were stratified according to the type of parameters guiding the management, resulting in two pre-specified groups of management strategies: haemodynamic-guided (i.e., driven by pulmonary artery and/or right ventricle pressures values) and impedance-guided (i.e, driven by the intrathoracic impedance value, directly related to the degree of pulmonary congestion)[21].

Data extraction and quality assessment

Data extraction of study design and features, patients' baseline characteristics, and outcomes was performed independently by two investigators (A.Z. and G.P.) 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 (A.Z. and G.P.) 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.[22]

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). Endpoint definitions of each study are reported in Supplementary material online, Table S4.

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 with the years of follow-up (for each arm, if available). Incidence rate ratios (IRRs) and the associated 95% confidence intervals (CIs) were used as metric of choice for treatment effects and were calculated using the mixed-effects Poisson regression model with random study effects. The heterogeneity between studies was evaluated using the Cochran's Q test, while consistency was measured by Higgins and Thompson I^2. Low heterogeneity was defined as an I^2 value less than 25%, moderate heterogeneity as a value of 25-50%, and high heterogeneity as a value greater than 50%. The potential presence of publication bias was assessed by visual inspection of funnel plots and using Egger test.

A main prespecified subgroup analysis was performed according to the type of monitoring strategy (haemodynamic or impedance) and findings were presented based on this analysis. Subgroup effects were compared using the Borenstein and Higgins test[23] and the credibility of subgroup differences was assessed by the ICEMAN tool, which consists of an eight-question survey that provides a four-levels rating of the credibility of subgroup-effect modification (very low credibility, low credibility, moderate credibility, and high credibility).[24]

A prespecified sensitivity analyses 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, two post-hoc sensitivity analyses included an analysis which added two studies testing a strategy of impedance-guided HF management with parameters monitored during in-clinic follow-up without remote monitoring systems (DOT-HF[25] and IMPEDANCE-HF[26]) and another analysis which excluded two studies reporting an outcome of first hospitalization instead of recurrent hospitalizations (COMPASS-HF[27], CONNECT-OptiVol[14]).

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.[28]

RESULTS

The comprehensive literature research retrieved 13496 articles. The PRISMA checklist and flow diagram are illustrated in Supplementary material online, Table S1 and Table S3. After screening, 8 RCTs were identified, with a total of 4347 patients randomly allocated to guided management (n=2173) or standard therapy (n=2174). The average follow-up duration was of 15 months, providing data on 5984 patient-years, including 3023 patient-years in the guided-management arm and 2961 patient-years in the standard-therapy arm. Four trials investigated a strategy of haemodynamic-guided management (n=2224 patients) during an average follow-up of 12 months (n=2362 patient-years) and four trials a strategy of impedance-guided management (n=2123 patients) during an average follow-up of 19 months (n=3620 patient-years). Key features of included trials and baseline characteristics of patients are summarized in the Table 1 and the Supplementary material online, Table S5 and Table S6. Trials testing a haemodynamic-guided management were characterized by frequent data revision (daily or weekly), while trials testing an impedance-guided management were characterized by an only-alert-based data revision (Supplementary material online, Table S5). All patients were receiving optimal medical therapy at the date of randomization (Supplementary material online, Table S7) and the clinical characteristics and therapeutic history of patients were similar in the two arms of each trial. The risk-of-bias assessment identified four studies at low risk of bias, three studies with some concerns, and one study at high risk of bias (Supplementary material online, Figure S1).

Main analyses

The primary outcome of all-cause death and hospitalizations for HF was significantly reduced with a strategy of congestion-guided HF management compared with standard therapy (IRR 0.88, 95% CI 0.78-0.99, p=0.034, I^2=47%; Figure 1). This result was driven by a reduction in the risk of hospitalizations for HF (IRR 0.85, 95% CI 0.75-0.97, p=0.016, I^2=45%; Figure 3), without a significant impact on all-cause death (IRR 0.96, 95% CI 0.80-1.16, p=0.697, I^2=0%; Figure 2). Treatment effects varied according to the type of monitoring strategy (haemodynamic or impedance) with subgroup analyses showing significant interactions for the primary outcome and the outcome of HF hospitalizations, with moderate credibility due to effect modification based on between-trial comparisons. A strategy of haemodynamic-guided management, compared with standard therapy, was associated with a reduction in the primary outcome (IRR 0.79, 95% CI 0.70-0.89, p<0.001, I^2=18%; Figure 1) and the hospitalizations for HF (IRR 0.76, 95% CI 0.67-0.86, p<0.001, I^2=20%; Figure 3), but no significant impact on all-cause death (IRR 0.93, 95% CI 0.72-1.21, p=0.594, I^2=0%; Figure 2). Conversely, a strategy of impedance-guided management did not reduce the risks of all-cause death (IRR 1.00, 95% CI 0.77-1.30, p=0.992, I^2=0%; Figure 2), HF hospitalizations (IRR 0.99, 95% CI 0.85-1.14, p=0.853, I^2=0%; Figure 3), and the composite of both (IRR 0.99, 95% CI 0.87-1.13, p=0.868, I^2=0%; Figure 1) in comparison to standard therapy.

Sensitivity and meta-regression analyses

At leave-one-out sensitivity analyses (Supplementary material online, Figure S2), no trial showed significant influence on the pooled estimate for all outcomes. Both the analyses which added DOT-HF[25] and IMPEDANCE-HF[26] (Supplementary material online, Table S8 and Figure S3) and the

analyses which excluded trials reporting an outcome of first hospitalization (COMPASS-HF[27] and CONNECT-OptiVol[14]; Supplementary material online, Figure S4) showed findings consistent with the main analyses.

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 online, Table S9). Funnel plots and Egger tests suggested no evidence of publication bias or small study effect (Supplementary material online, Figure S5).

DISCUSSION

This comprehensive systematic review and meta-analysis address the challenging task of guiding the management of HF according to device-based remotely monitored congestion markers. The results of this meta-analysis of 8 RCTs involving 4347 patients with HF show that, compared with standard therapy, guided management according to device-based remotely monitored preclinical congestion markers is associated with a reduced risk of the composite of all-cause death and hospitalizations for HF, mainly driven by a reduction in HF hospitalizations. Findings varied according to the type of parameters monitored (Graphical Abstract): (1) a strategy of hemodynamic-guided management was associated with a reduction in the composite of all-cause death and hospitalizations for HF, driven by a reduction in hospitalizations without a significant mortality

reduction; (2) a strategy of impedance-guided management was not able to provide a significant reduction in the risks of death, HF hospitalizations, and the composite endpoint.

These results reflect the pathogenesis of HF progression from a compensated and euvolemic state to an acutely and volume overloaded state, which occurs through various steps beginning about 30 days before the development of clinical signs.[8] A slight increase in filling and intracardiac pressures occurs early in this transition phase,[9] followed by a compensatory autonomic response characterized by sympathetic activation and vagal withdrawal, detectable by changes in several cardiac electrical activity features with varying predictive values (e.g., onset of atrial fibrillation or ventricular tachyarrhythmias, reduction of heart rate variability, and of biventricular pacing rate).[29–31] Then pulmonary vascular capacitance gets overwhelmed with initial pulmonary fluid accumulation, which can be detected by a reduction in intrathoracic impedance.[10,21] Finally, this process results in generalized fluid overload with progressive development of symptoms and signs of decompensation leading to hospitalization.

In line with the pathophysiological and clinical findings, the use of intrathoracic impedance as a unique monitoring parameter to guide the management is limited by the late onset of pulmonary congestion.[32] In contrast, a strategy of haemodynamic monitoring as a tool for continuous optimization of care appears to offer reasonable effectiveness in directing HF management because an increase in intracardiac or pulmonary artery pressures represent an early sign of worsening heart failure which allows a prompt and targeted therapeutic response. However, it should be emphasized that the frequency of data revision (daily or weekly for haemodynamic-guided strategy and only-alert-based for impedance-guided management) may have been a potential treatment modifier,

influencing the effects provided by the impedance-guided management strategy. Future studies are needed to explore this inference.

Previous meta-analyses suggested a marginal reduction in the risk of HF hospitalizations with a strategy of haemodynamic-guided management and no benefits with an heterogeneous group of strategies of impedance-guided management. Our meta-analysis, by adopting a patient-years approach and strict selection criteria of RCTs, suggested a substantial difference in the effects of the different strategies of congestion-guided management according to the monitored parameters.[17–19] Although haemodynamic-guided management reduced the incidence of HF hospitalizations, it did not result in a significant mortality reduction over a 12-month follow-up period. However, since a reduction in HF hospitalizations or pulmonary artery pressure was previously associated with long-term mortality benefits,[33,34] a longer follow-up time and/or a larger sample size might be able to provide this finding, as already confirmed by real-world data.[35] Furthermore, the inclusion of a proportion of patients with LVEF greater than 40% in two trials investigating haemodynamic-guided management (22% of patients in CHAMPION trial[11] and 47% of patients in GUIDE-HF trial[12]) should not be overlooked. Although a guided management according to haemodynamic parameters in this subgroup is able to reduce HF hospitalizations as well as in patients with lower LVEF,[36] its impact on mortality is still uncertain and under investigation, likely affecting overall estimates of the mortality benefit provided by this monitoring strategy.

Some trials, taken individually, did not provide sufficient evidence to support the widespread use of device-based congestion-guided HF management, as reported by recent guidelines and consensus statements.[2,37] However, the use of unreliable decompensation markers, the lack of adequate or

prompt therapeutic response, and some design limitations may have skewed trials results. Major pitfalls included insufficient statistical power to detect significant differences between arms, inadequate transmission of monitored data, and/or poor treatment reaction.[13,14,38,39] Furthermore, frequent clinical monitoring of control arms, sometimes by non-invasive telemonitoring, may have underestimated the favourable effect provided by the guided management. Indeed, real-world data broadly support the routine use of monitored haemodynamic parameters in guiding HF management.[35] Finally, as predicted by clinicians learning curves after implementation of remote monitoring systems, the large-scale use of these tools will optimize their performance by gradually enhancing the targeted treatment response.

Our findings must be interpreted in light of public health and economic priority, with HF hospitalizations representing the main financial burden to healthcare systems and one of the strongest predictors of mortality.[4] The primary outcome of our meta-analysis, as a surrogate of keeping patients alive and out of the hospital, address both sides of this issue.

The inevitable costs deriving from the implementation of these devices (eg, CardioMEMS listed as $17,750 with Medicare)[40], the use of monitoring algorithms, and the development of telemedical evaluation units are important issues to be addressed. Some analyses suggested that haemodynamic-guided management may be cost-effective with a favourable clinical and economic impact.[41,42] However, it should be recognized that the costs of deploying telemedical evaluation units have been roughly estimated and might be a major burden for health systems. As a result, additional data on device maintenance and monitoring costs are needed to guide future global economic assessments.

The success of remote monitoring strategies will depend on the optimal data transmission, as well as on the physicians' clinical attitude to telemonitoring strategies and on the patients' engagement and acceptance. Machine-learning systems could address these limitations, implementing virtual coaching systems for both healthcare professionals and patients.[43] Future RCTs will provide further data on the effectiveness of guided management according to parameters monitored through a wide range of devices.[44]

Limitations

Our study has some limitations. First, the lack of patient-level data has foreclosed the assessment of potential treatment modifiers. Particularly, two trials testing haemodynamic-guided management included a proportion of patients with LVEF more than 40%, and it cannot be ruled out that this may have influenced the impact on mortality of this monitoring strategy.[11,12] Second, two trials assessed an endpoint of first hospitalizations instead of recurrent hospitalizations. However, the results of removing those trials were consistent with the main analysis. Three, some studies have not reported or are heterogeneous in defining the outcome of HF hospitalizations, limiting results reliability. Fourth, one study may have enrolled a small proportion of patients without HF.[14] However, at leave-one-out sensitivity analysis, the exclusion of this trial provided results consistent with the main analysis. Fifth, the use of patient-years approach may have led to a bias due to partially reported arm-specific follow-up times. However, the inclusion of only RCTs and the use of the Poisson regression model reduced the risk of this bias, supporting results validity.[45]

CONCLUSION

Compared to standard therapy, a device-based remote monitoring strategy for haemodynamic-guided management of patients with HF is associated with a reduction in the composite of all-cause death and hospitalizations for HF, driven by a reduction in hospitalizations without a significant mortality benefit. Contrarily, an impedance-guided management was not able to provide significant benefits. Further research will determine whether haemodynamic-based remote monitoring strategy is cost-effective in guiding the management of patients with HF.

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CONFLICT OF INTERESTS

CT discloses to have been involved in advisory board meetings or having received speaker's fees from Abbott, Abiomed, Biotronic. FB discloses to have been involved in advisory board meetings

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DATA AVAILABILITY

The data underlying this article are available in the article and in Supplementary material online.

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FIGURE TITLES AND LEGENDS

Figure 1. Title: Guided management versus standard therapy for the primary outcome

Legend Figure 1: CI=confidence interval; IRR=incidence rate ratio; Time=patient-years.

Figure 2. Title: Guided management versus standard therapy for the all-cause death outcome

Legend Figure 2: CI=confidence interval; IRR=incidence rate ratio; Time=patient-years.

Figure 3. Title: Guided management versus standard therapy for the HF hospitalizations outcome

Legend Figure 3: CI=confidence interval; IRR=incidence rate ratio; Time=patient-years.

Graphical Abstract. Title: Summary effect estimates for different strategies of guided management versus standard therapy related to pathogenesis of worsening heart failure

Legend Graphical Abstract: CI=confidence interval; IRR=incidence rate ratio.

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

	Year	Device	Number of patients			Major parameters guiding management		Type of monitoring	Follow-up
			Overall	Guided management	Control	Guided management	Control		
CHAMPION[11]	2016	CardioMEMS HF System	550	270	280	Pulmonary artery pressures	Non-invasive telemonitoring	Haemodynamic	18 months
COMPASS-HF[27]	2008	Chronicle ICHM	274	134	140	Pulmonary artery and right ventricular diastolic pressures	Non-invasive telemonitoring	Haemodynamic	6 months
CONNECT-OptiVol[14]	2015	ICD/CRT	176	87	89	Intrathoracic impedance	Usual care	Impedance	15 months
GUIDE-HF[12]	2021	CardioMEMS HF System	1000	497	503	Pulmonary artery pressures	Non-invasive telemonitoring	Haemodynamic	12 months
[illegible]T-CHF[13]	2016	ICD/CRT	80	41	39	Intrathoracic impedance	Usual care	Impedance	12 months
MORE-CARE[38]	2017	CRT	865	437	428	Intrathoracic impedance and atrial tachyarrhythmia	Usual care	Impedance	24 months
OptiLink HF[46]	2016	ICD/CRT	1002	505	497	Intrathoracic impedance	Usual care with device data accessible in the clinic	Impedance	23 months
REDUCEhf[39]	2011	Chronicle ICD	400	202	198	Pulmonary artery and right ventricular diastolic pressures	Non-invasive telemonitoring	Haemodynamic	12 months

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

All-cause death and Hospitalizations for Heart Failure

Study	Guided Events	Guided Time	Standard Events	Standard Time	IRR	95%−CI
Haemodinamyc						
CHAMPION	232	405	343	420	0.70	[0.59; 0.83]
COMPASS−HF	50	67	68	70	0.77	[0.53; 1.11]
GUIDE−HF	225	497	262	503	0.87	[0.73; 1.04]
REDUCEhf	79	202	87	198	0.89	[0.66; 1.21]
Fixed effect model					**0.79**	**[0.71; 0.88]**
Random effects model					**0.79**	**[0.70; 0.89]**
Heterogeneity: I^2 = 18%, τ^2 = 0.0020, χ^2_3 = 3.67 (p = 0.30)						
Test for effect in subgroup (fixed effect): z = −4.34 (p < 0.001)						
Test for effect in subgroup (random effects): z = −3.81 (p < 0.001)						
Impedance						
CONNECT−OptiVol	28	109	28	111	1.02	[0.60; 1.72]
LIMIT−CHF	15	41	9	39	1.59	[0.69; 3.62]
MORE CARE	151	707	137	696	1.09	[0.86; 1.37]
OptiLink HF	279	995	281	924	0.92	[0.78; 1.09]
Fixed effect model					**0.99**	**[0.87; 1.13]**
Random effects model					**0.99**	**[0.87; 1.13]**
Heterogeneity: I^2 = 0%, τ^2 = 0, χ^2_3 = 2.57 (p = 0.46)						
Test for effect in subgroup (fixed effect): z = −0.17 (p = 0.868)						
Test for effect in subgroup (random effects): z = −0.17 (p = 0.868)						
Fixed effect model					**0.86**	**[0.80; 0.94]**
Random effects model					**0.88**	**[0.78; 0.99]**

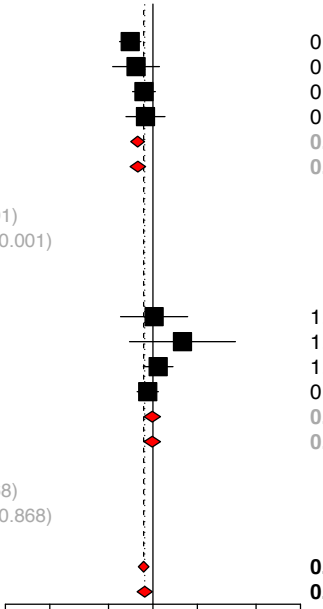
Heterogeneity: I^2 = 47%, τ^2 = 0.0099, χ^2_7 = 13.22 (p = 0.07)

Test for overall effect (fixed effect): z = −3.45 (p < 0.001)

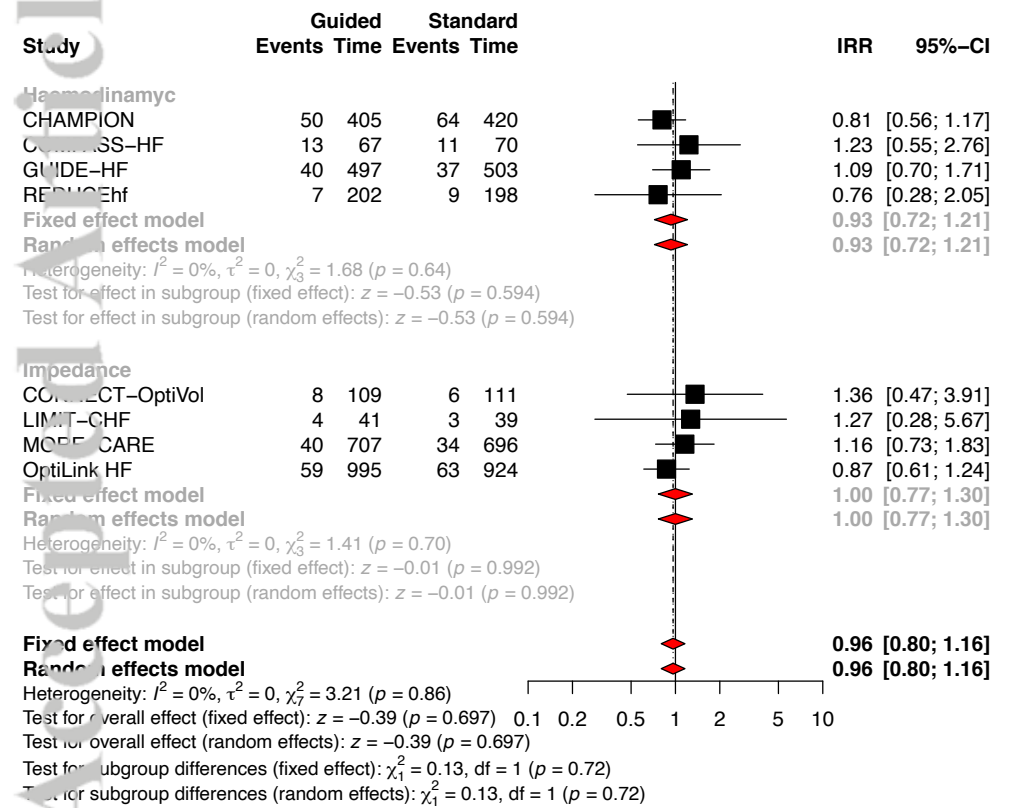
Test for overall effect (random effects): z = −2.12 (p = 0.034)

Test for subgroup differences (fixed effect): χ^2_1 = 7.08, df = 1 (p < 0.01)

Test for subgroup differences (random effects): χ^2_1 = 6.20, df = 1 (p = 0.01)



All-cause death



Hospitalizations for Heart Failure

Study	Guided Events	Guided Time	Standard Events	Standard Time	IRR	95%−CI
Hemodinamyc						
CHAMPION	182	405	279	420	0.68	[0.56; 0.82]
COMPASS−HF	37	67	57	70	0.68	[0.45; 1.03]
GUIDE−HF	185	497	225	503	0.83	[0.69; 1.01]
REDUCEhf	72	202	78	198	0.90	[0.66; 1.25]
Fixed effect model					0.76	[0.68; 0.86]
Random effects model					0.76	[0.67; 0.86]
Heterogeneity: I^2 = 20%, τ^2 = 0.0008, χ^2_3 = 3.76 (p = 0.29)						
Test for effect in subgroup (fixed effect): z = −4.53 (p < 0.001)						
Test for effect in subgroup (random effects): z = −4.29 (p < 0.001)						
Impedance						
CONNECT−OptiVol	20	109	22	111	0.93	[0.51; 1.70]
LIMIT−CHF	11	41	6	39	1.74	[0.64; 4.72]
MORE−CARE	111	707	103	696	1.06	[0.81; 1.39]
OptiLink HF	220	995	218	924	0.94	[0.78; 1.13]
Fixed effect model					0.99	[0.85; 1.14]
Random effects model					0.99	[0.85; 1.14]
Heterogeneity: I^2 = 0%, τ^2 = 0, χ^2_3 = 1.87 (p = 0.60)						
Test for effect in subgroup (fixed effect): z = −0.18 (p = 0.853)						
Test for effect in subgroup (random effects): z = −0.18 (p = 0.853)						
Fixed effect model					**0.84**	**[0.77; 0.92]**
Random effects model					**0.85**	**[0.75; 0.97]**

Heterogeneity: I^2 = 45%, τ^2 = 0.0110, χ^2_7 = 12.79 (p = 0.08)

Test for overall effect (fixed effect): z = −3.66 (p < 0.001)

Test for overall effect (random effects): z = −2.42 (p = 0.016)

Test for subgroup differences (fixed effect): χ^2_1 = 7.28, df = 1 (p < 0.01)

Test for subgroup differences (random effects): χ^2_1 = 6.94, df = 1 (p < 0.01)