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CARDIOVASCULAR CARE (L ROEVER, SECTION EDITOR)

Effects of Telemonitoring and Hemodynamic Monitoring on Mortality in Heart Failure: a Systematic Review and Meta-analysis

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Abstract

Purpose of Review To examine the effectiveness of telemonitoring and hemodynamic monitoring devices in reducing mortality rates in heart failure. PubMed and Cochrane Library were searched to 1 May 2017 for randomized controlled trials and real-world studies investigating the effects of telemonitoring or hemodynamic monitoring on mortality in heart failure.

Recent Findings Heart failure is associated with increased mortality. Telemonitoring and hemodynamic monitoring have been shown to reduce mortality rates in some studies but not others.

Summary Fifty-two and five publications on telemonitoring and hemodynamic monitoring were included. In 23,233 patients (mean age 70 years, mean follow-up 12 ± 10 months), telemonitoring reduced all-cause mortality by 22% (HR = 0.78; 95% confidence interval (CI), 0.74–0.83; $P < 0.0001$). In 1224 patients (mean age 59 years, mean follow-up 12 ± 6 months), wireless hemodynamic monitoring had no effect on all-cause mortality (HR = 0.87; 95% CI, 0.61–1.25; $P > 0.05$). Overall, telemonitoring but not hemodynamic monitoring reduced mortality in heart failure.

Keywords Telemonitoring · Hemodynamic monitoring · Heart failure · Mortality

Introduction

Heart failure (HF) is a complex syndrome and a major public health problem worldwide, with a prevalence of more than 5.8 million in the USA and more than 23 million worldwide [1], placing significant economic burdens on the global healthcare system. For example, it is estimated that HF accounts for 1 to 2% of the healthcare expenditure, of which 75% is due to hospital admissions [2]. Moreover, mortality remains high for this condition, with a four- to eightfold increase compared with age-matched individuals without HF [3]. In addition to guideline-directed therapy for HF, implantable technologies for remote monitoring of intracardiac hemodynamics have been developed in an attempt to reduce adverse outcomes. Telemonitoring involves telephone-based surveillance and management [4] while implantable wireless monitors have been created to measure and record hemodynamic parameters remotely. Currently, three devices are available in the market: CardioMEMS, Chronicle, and HeartPOD, which can measure pulmonary arterial pressure, right ventricular pressure, and left atrial pressure, respectively.

Several systematic reviews with meta-analysis of randomized controlled trials (RCTs) on the effects of telemonitoring on mortality rates in HF have been performed. One study summarized results from 11 RCTs, demonstrating no significant effects of telemonitoring on mortality rates [5••]. By contrast, another study pooled data from 41 RCTs and demonstrated a significant reduction in all-cause mortality rates [6]. Another meta-analysis found a 15 to 52% reduction in mortality [7]. In the modern era of digital health care, the role of telemonitoring in reducing overall mortality in HF patients still remains unclear. Also, whether remote monitoring can be utilized as a reasonable substitute for doctors' office visits

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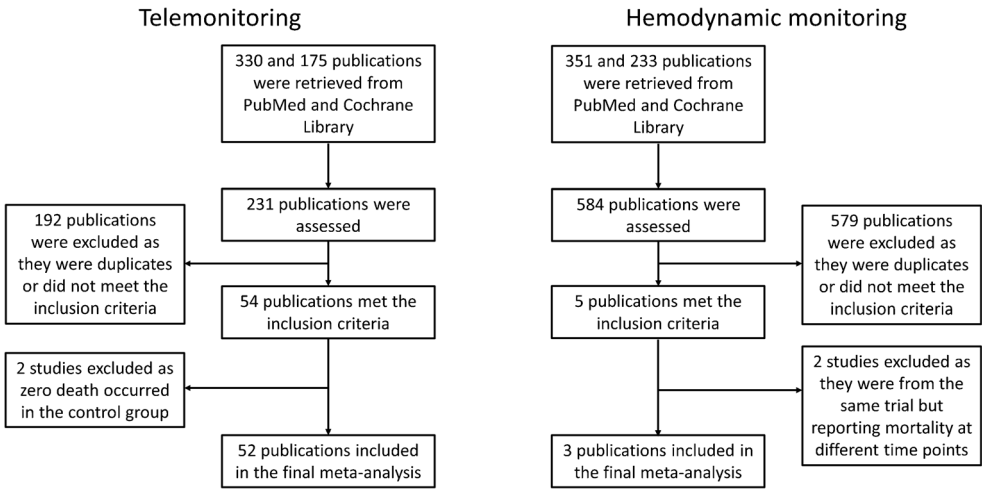

Fig. 1 Flow diagram of the study selection process

and physical examination remains to be determined. The aim of this updated meta-analysis is to include not only randomized controlled trials but also real-world studies that have examined the effects of both telemonitoring and hemodynamic monitoring on mortality outcomes in heart failure.

Methods

Search Strategy, Criteria for Inclusion, and Quality Assessment

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [8]. It has been registered with PROSPERO. PubMed and Cochrane Library were searched up to 16 April 2018, with no language restriction, for studies that investigated mortality rates in heart failure using the following terms: "telemonitoring" AND "heart failure" and "hemodynamic monitoring" AND "heart failure" separately. The following inclusion criteria were applied: (i) the study design was a case-control, prospective or retrospective observational study, or randomized controlled trial conducted in humans and (ii) mortality rates, including all-cause, cardiovascular-related, and heart failure-specific, were reported.

Quality assessment of randomized controlled trials using the Jadad scale (Oxford quality scoring system) (Supplementary Tables 1 and 2 for telemonitoring and hemodynamic monitoring, respectively), and of case-control and cohort studies, was conducted using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Supplementary Table 3) [9]. The NOS evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following domains were assessed: (a) representativeness of the exposed cohort; (b) selection of the nonexposed cohort; (c) ascertainment of exposure; (d) demonstration that outcome of interest was not present at the start of the study; (e) comparability of cohorts on the basis of the design or analysis; (f) assessment of outcomes; (g) follow-up period sufficiently long for outcomes to occur; and (h) adequacy of follow-up of cohorts. This scale ranged from zero to nine stars, which indicated that studies were graded as poor quality if they met < 5 criteria, fair if they met 5 to 7 criteria, and good if they met > 8 criteria. The Jadad score assessed the quality by the following criteria of (a) randomization, (b) allocation concealment, (c) double blinding, and (d) withdrawal and dropouts. The total score is 7; scores 1 to 3 indicate low quality and 4 to 7 high quality.

Data Extraction and Statistics

Data from the different studies were entered in a spreadsheet template in Microsoft Excel. All potentially relevant entries were retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. Two reviewers (GT and MG) independently reviewed each included study and disagreements were resolved by adjudication with input from a third reviewer (TL). The extracted data included (i) publication details: last name of the first author, publication year, and locations; (ii) study design (cohort study or randomized controlled trial); (iii) follow-up duration; (iv) type of mortality endpoints (all-cause, cardiac-related, or heart failure–related); (v) quality score; and (vi) the characteristics of the population including sample size, age, and gender. The endpoints for this meta-analysis were mortality rates. Multivariate-adjusted hazard ratios (HRs) or relative risks (RRs) with 95% confidence interval (CI) were extracted from each study. When values from multivariate analysis were not available, those from the univariate analysis were used. When the latter was not provided, raw mortality data were used to calculate unadjusted risk estimates. The pooled adjusted risk estimates from each study as the HR/OR values with 95% CI were presented.

Table 1 Characteristics of the 52 studies on telemonitoring included in this meta-analysis

First author/year	Study design	Sample size (*n*)	Age	SD	% Male	Ejection fraction (%)	Endpoints	Follow-up (months)	Variables in multivariate model
Herold 2017	Cohort	5602	74	13	54	24	All-cause mortality	24	(Univariate)
Sardu 2016	RCT	183	72	7	76	<35	All-cause mortality, cardiac mortality	12	Age, chronic kidney disease, hypercholesterolaemia, LVEF, NYHA class
Van Spall 2016	RCT	1437	73	–	54	–	All-cause mortality	1, 6	(Univariate)
Martín-Lesende 2016	Cohort	83	81	6	58	–	All-cause mortality	60	(Univariate)
Ong 2016	RCT	1437	73	–	54	43	All-cause mortality	3, 6	Age, sex, race/ethnicity, insurance, comorbidities based on the Health Care Utilization Project methods, 6 years and a quarter of enrollment, social isolation as measured by the Lubben Social Network Scale score, 31 and income level.
Kraai 2016	RCT	177	69	16	37	27	All-cause mortality	9	(Univariate)
Smolis-Bąk 2016	Cohort	52	62	9	90	25	All-cause mortality	18	(Univariate)
Kao 2016	Cohort	1246	78	12	54	–	All-cause mortality	36	(Univariate)
Idris 2015	RCT	28	63	–	39	23	All-cause mortality	3, 6	(Univariate)
Pedone 2015	RCT	90	80	7	39	46	All-cause mortality	6	(Univariate)
Agboola 2015	Cohort	348	77	15	59	50	All-cause mortality	12	Age, gender, race, ejection fraction, and New York Heart Association classification (NYHA)
Bekelman 2015	RCT	384	68	14	97	–	All-cause mortality	12	(Univariate)
Dierckx 2015	Cohort	333	71	12	–		All-cause mortality	36	Age, heart rate, body mass index (BMI), log-transformed N-terminal pro B-type natriuretic peptide (NTproBNP), estimated glomerular filtration rate (eGFR), hemoglobin, sodium, cardiac resynchronization therapy (CRT), angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin-receptor blockers (ACE-I/ARB) at baseline and New York Heart Association (NYHA) class.
Kenealy 2015	RCT	98	72	20	–	36	All-cause mortality	6	Age, gender
Hindricks 2014	RCT	664	66	13	81	26	All-cause mortality	11	Use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (the only substantial imbalance between groups at randomization)
Giacomelli 2014	RCT	285	80	–	60	–	Combined all-cause mortality and hospitalization	9	(Univariate)
Martín-Lesende 2013	RCT	58	81	8	59	–	All-cause mortality	6, 12	(Univariate)
Krum 2013	RCT	405	73	15	63	36	All-cause mortality	12	Age, gender, practice region (RRMA), and baseline NYHA class
Sabatier 2013	RCT	90	–	–	–	–	All-cause mortality, cardiovascular mortality	3	(Univariate)
Boyne 2012	RCT	382	71	11	59	36	All-cause mortality, cardiovascular mortality	12	Age, NYHA classification, and urea
Dendale 2012	RCT	160	76	10	65	35	All-cause mortality	6	(Univariate)
Koehler 2012	RCT	670	67	15	86	27	All-cause mortality, cardiovascular mortality	26	LVEF, baseline PHQ score
Kurtz 2011	Cohort	138	68	17	78	32	Cardiovascular mortality	12	Age, state of residence, presence of various comorbid conditions, and prior cardiac events including coronary artery bypass surgery
Wade 2011	RCT	316	77	10	53	–	All-cause mortality	6	Age, sex, date of randomization, locality, comorbid conditions, prior healthcare events, and risk.
Domingo 2011	RCT	92	66	12	71	36	All-cause mortality	12	(Univariate)
Howlett 2011	RCT	122	67	–	65	46	All-cause mortality	12	(Univariate)
Chaudhry 2010	RCT	1653	61	16	58	–	All-cause mortality	9	(Univariate)
Antonicelli 2010	RCT	57	78	7	58	–	All-cause mortality	12	(Univariate)
Peters-Klimm 2010	RCT	199	70	14	72	–	All-cause mortality	12	(Univariate)
Goode 2009	RCT	201	70	11	70	24	All-cause mortality, cardiac mortality	16	(Univariate)
Soran 2008	RCT	315	76	10	31	24	All-cause mortality, cardiovascular mortality	6	New York Heart Association class, β-blocker use at baseline, sex, and Na levels
Antonicelli 2008	RCT	57	78	10	58	36	All-cause mortality	12	(Univariate)
Schwarz 2008	RCT	102	78	–	48	–	All-cause mortality	3	–
Kashem 2008	RCT	48	54	15	73	26	All-cause mortality	12	(Univariate)
Sisk 2006	RCT	406	59	19	54		All-cause mortality	12	(Univariate)
Riegel 2006	RCT	134	72	11	46	43	All-cause mortality	6	(Univariate)
GESICA Investigators 2005	RCT	1518	65	13	71	–	All-cause mortality	16	NYHA class, age, baseline treatment, comorbidity, and systolic dysfunction
Dunagan 2005	RCT	151	–	–	47		All-cause mortality	12	Severely impaired LV function, NYHA class, use of target or high doses of ACE inhibitor
Cleland 2005	RCT	253	67	16	53	25	All-cause mortality, heart failure mortality	8	Age, NT proBNP, body mass index, systolic and diastolic blood pressure, hemoglobin, sodium, urea, creatinine, NYHA functional classification, loop and potassium-sparing diuretics, ACE inhibitors, beta blockers

Table 1 (continued)

First author/year	Study design	Sample size (*n*)	Age	SD	% Male	Ejection fraction (%)	Endpoints	Follow-up (months)	Variables in multivariate model
Capomolla 2004	RCT	133	57	10	47	29	All-cause mortality, heart failure mortality	12	(Univariate)
Galbreath 2004	RCT	1069	71	10	71	54	All-cause mortality	6, 18	(Univariate)
DeBusk 2004	RCT	462	72	11	51	–	All-cause mortality	12	(Univariate)
Goldberg 2003	RCT	208	59	15	68	< 35	All-cause mortality	6	(Univariate)
Laramee 2003	RCT	287	71	12	54	–	All-cause mortality	1.5	(Univariate)
McDonald 2002	RCT	98	71	10	66	37	All-cause mortality	3	(Univariate)
Riegel 2002	RCT	358	72	12	49	43	All-cause mortality	3, 6	(Univariate)
Kasper 2002	RCT	200	62	20	33	27	All-cause mortality	6	(Univariate)
Krumholz 2002	RCT	88	76	13	57	38	All-cause mortality	12	(Univariate)
Jerant 2001	RCT	25	70	16	48	–	All-cause mortality	2	(Univariate)
Blue 2001	RCT	165	75	12	58	–	All-cause mortality	12	(Univariate)
Cordisco 1999	Cohort	81	53	11	75	–	All-cause mortality	12	(Univariate)
Gattis 1999	RCT	181	67	18	68	30	All-cause mortality, heart failure mortality	6	(Univariate)

RCT, randomized controlled trial; *HF*, heart failure

Heterogeneity between studies was determined using Cochran's Q, which is the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which is the percentage of the variability in effect estimates resulting from heterogeneity. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if $I^2 < 50\%$; otherwise, the random-effects model using the inverse variance heterogeneity method was selected. To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time was conducted. Subgroup analyses based on time points or type of telemonitoring or hemodynamic monitoring were performed. Short-term was defined as those occurring within 6 months, whereas long-term was defined as 12 months or longer. Where a study reported effective estimates at successive time points, the longer time point was used. Funnel plots, the Begg and Mazumdar rank correlation test, and Egger's test were used to assess for publication bias.

Results

A flow diagram detailing the search strategy and study selection is shown in Fig. 1. On telemonitoring, a total of 371 and 175 entries were retrieved from PubMed and Cochrane Library, of which 37 publications were included. For hemodynamic monitoring, a total of 351 and 233 entries were retrieved from the same databases, with five articles included in this meta-analysis.

Telemonitoring

A total of 54 studies satisfied the inclusion criteria [4, 10–47]. However, two of these found no deaths in the control group, preventing us to calculate a hazard ratio or odds ratio, and were excluded [24, 31]. Therefore, 52 studies were included in the final meta-analysis [4, 10–23, 25–30, 32–47]. A total of 23,233 patients (mean age, 70 years old; 61% male) were included. The baseline characteristics of these studies are listed in Table 1. The parameters determined by telemonitoring in each included study are shown in Supplementary Table 4. Forty-four studies were randomized controlled trials and eight were cohort studies. The mean follow-up duration was 12 ± 10 months. Telemonitoring reduced all-cause mortality by 22% (HR, 0.78; 95% confidence interval, 0.74 to 0.83; $P < 0.0001$; Fig. 2). Cochran's Q value was greater than the degrees of freedom (52 vs. 51), suggesting the true effect size was different among the various studies. Moreover, I^2 took a value of 3%, indicating the presence of little heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the

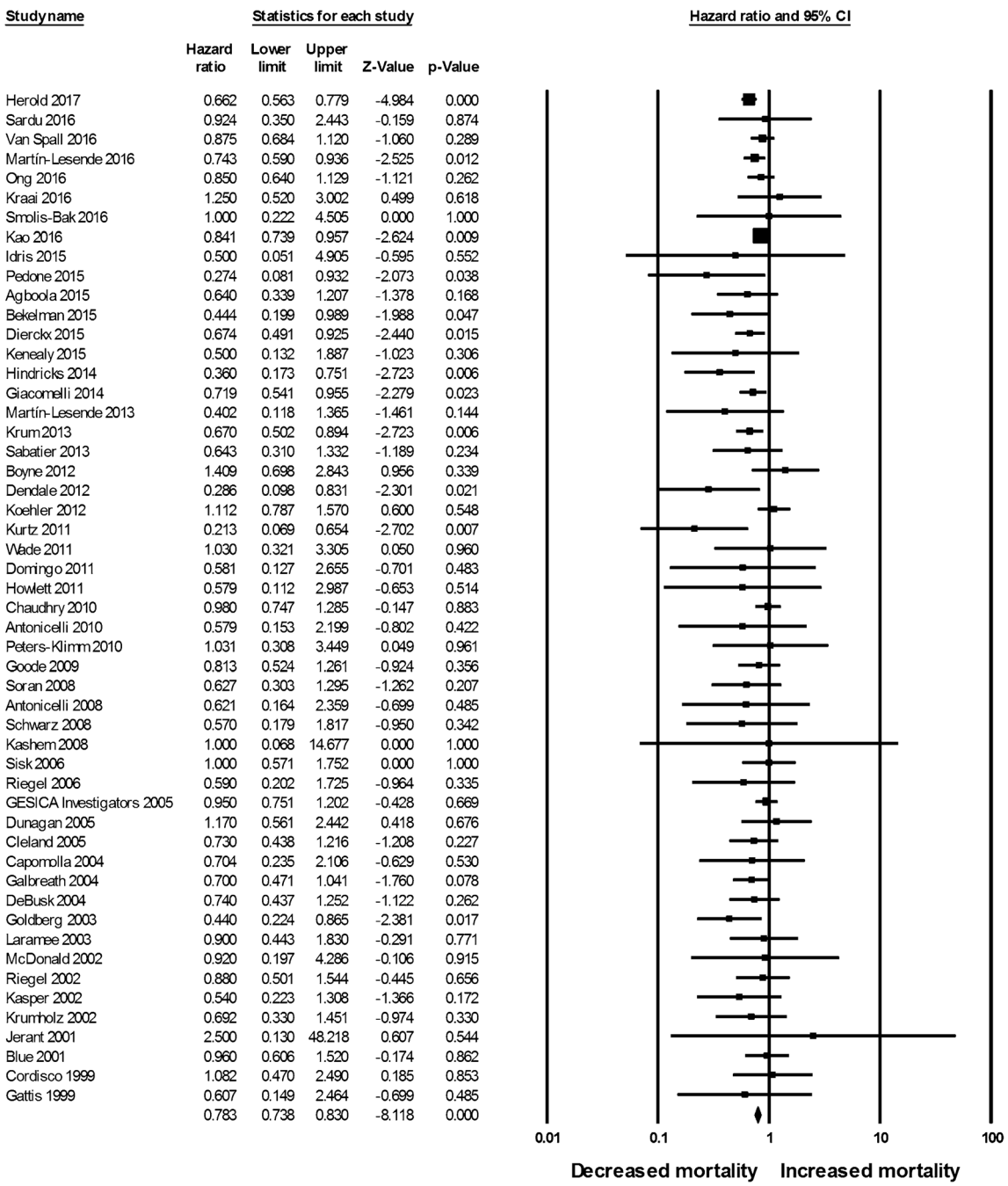

Fig. 2 Forest plot demonstrating the association between telemonitoring and mortality in heart failure

pooled hazard ratio (Supplementary Figure 1). Funnel plot plotting standard errors or precision against the logarithms of the hazard ratios is shown in Supplementary Figure 2 and Supplementary Figure 3, respectively. The Begg and Mazumdar rank correlation test suggested no significant publication bias (Kendal's Tau value = − 0.10, $P > 0.05$). Egger's test demonstrated no significant asymmetry (intercept − 0.35, t value 1.62; $P > 0.05$). Nineteen studies examined the effects of telemonitoring on short-term mortality (< = 6 months, mean = 5 ± 2 months), with our meta-analysis showing a reduction of 25% (HR = 0.75; CI, 0.65 to 0.86; $I^2 = 0\%$; $P < 0.0001$; Fig. 3). Moreover, 30 studies reported on long-term mortality (> = 12 months; mean = 17 ± 11 months), showing a 22% reduction with telemonitoring (HR = 0.78; CI, 0.73 to 0.84; $I^2 = 4\%$; $P < 0.0001$; Fig. 4). Subgroup analysis based on study design was also performed. The pooled hazard ratio from 44 RCTs was 0.81 (CI, 0.75 to 0.88; $I^2 = 0\%$; $P < 0.0001$; Fig. 5), whereas that of from the eight cohort studies was comparable, at 0.75 (0.69 to 0.82; $I^2 = 40\%$; $P < 0.0001$; Fig. 6).

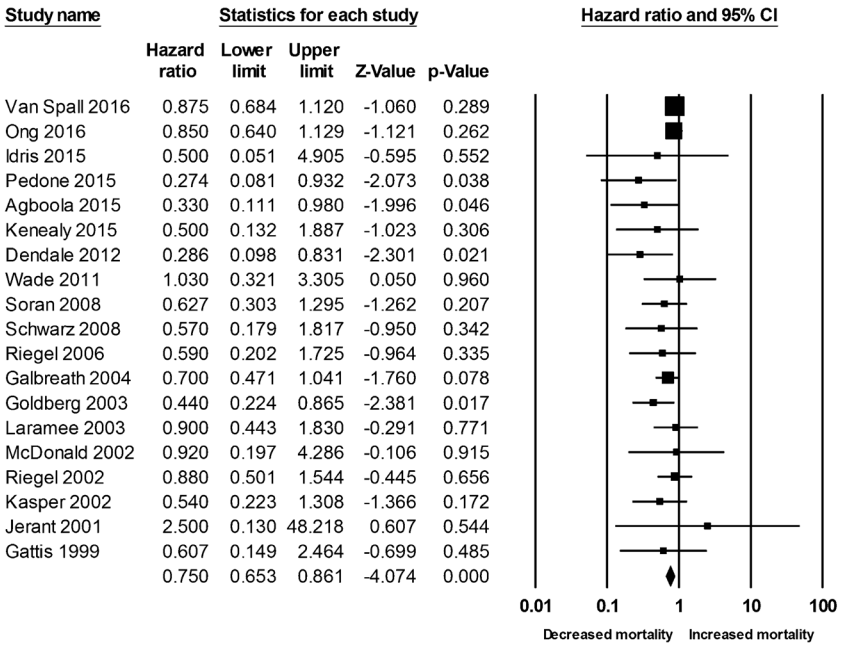

Fig. 3 Forest plot demonstrating the association between telemonitoring and short-term mortality in heart failure

Hemodynamic Monitoring

For hemodynamic monitoring, five studies based on data obtained from three clinical trials (CHAMPION for CardioMEMS, REDUCEhf and COMPASS-HF for Chronicle) were included [48–52]. Two studies were excluded as they reported mortality rates in the same patient cohort at different time points for the same trial (CHAMPION) [48, 49].

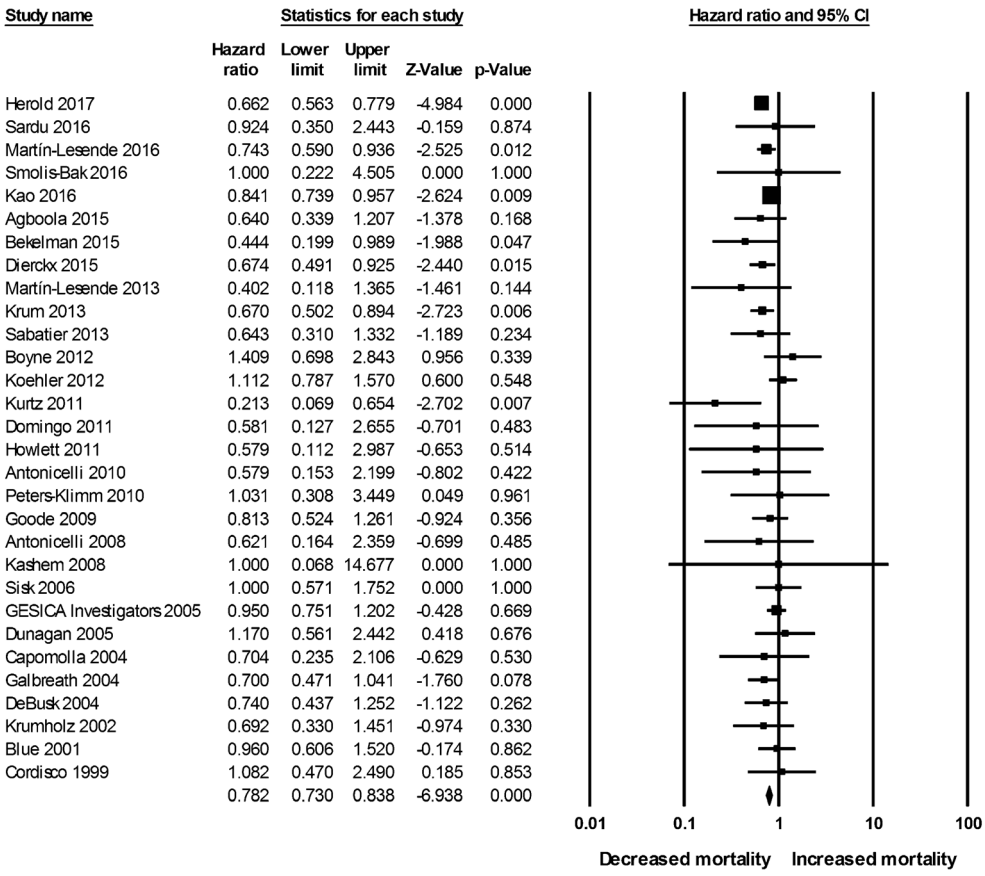

Fig. 4 Forest plot demonstrating the association between telemonitoring and long-term mortality in heart failure

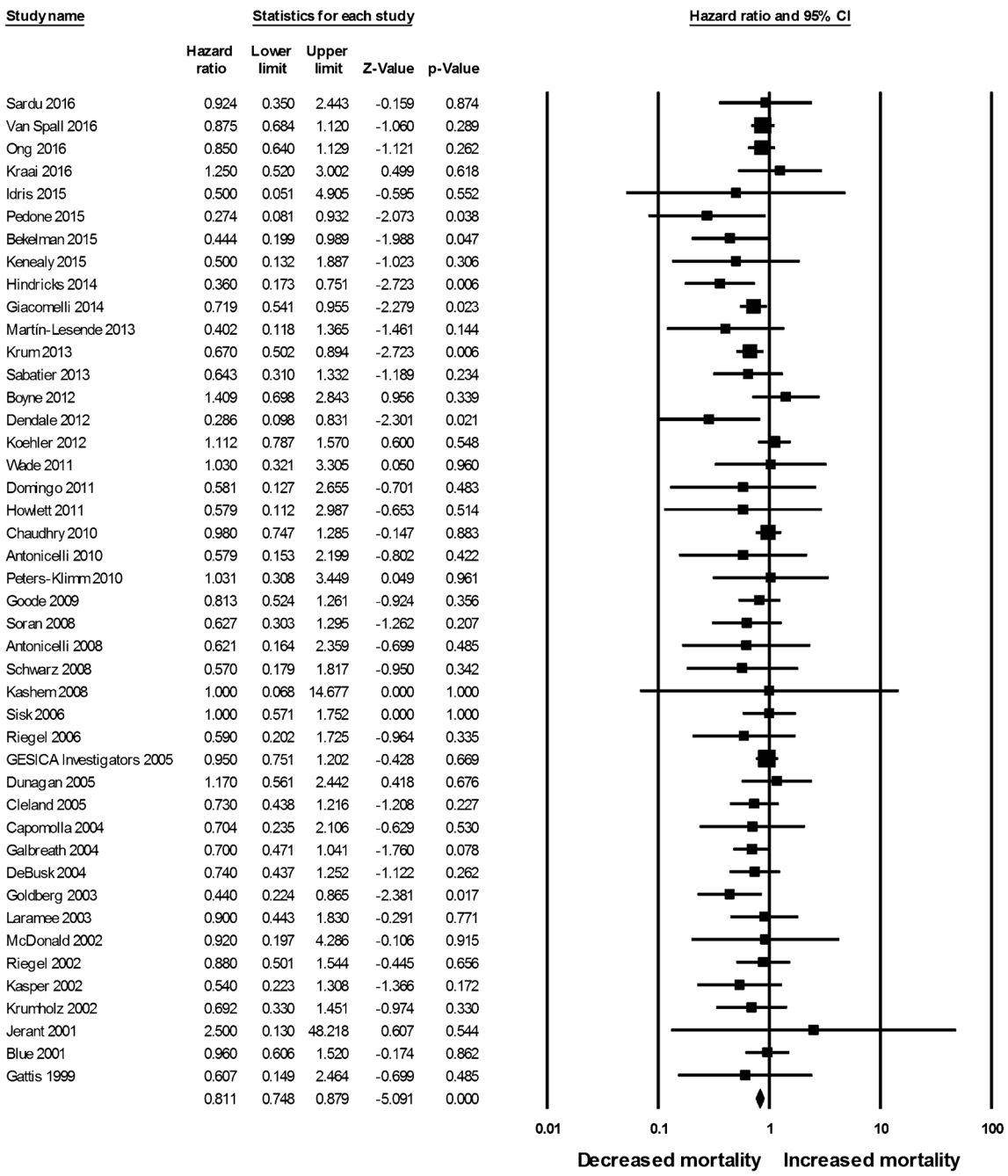

Fig. 5 Forest plot demonstrating the association between telemonitoring and mortality in heart failure from randomized controlled trials

Fig. 6 Forest plot demonstrating the association between telemonitoring and mortality in heart failure from cohort studies

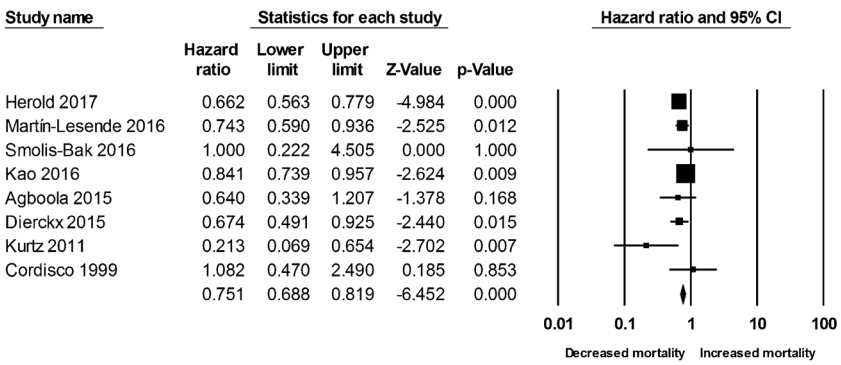

Table 2 Characteristics of the 3 studies on hemodynamic monitoring included in this meta-analysis

First author/year	Study design	Population	Type of hemodynamic monitoring	Sample size (*n*)	Age	SD	% Male	Ejection fraction (%)	Endpoints	Follow-up (months)	Variables in multivariate model
Adamson 2016	RCT	HF	Pulmonary arterial pressure	245	73	8	–	–	All-cause mortality	17	(Univariate)
Adamson 2011	RCT	HF	Right ventricular pressure	400	55	21	34	23	All-cause mortality	12	(Univariate)
Bourge 2008	RCT	HF	Right ventricular pressure	274	58	19	65	33	HF	6	(Univariate)

Therefore, three studies including a total of 1224 patients (mean age, 59 years old; 58% male) were meta-analyzed. The baseline characteristics of these studies are listed in Table 2. The mean follow-up duration was 12 ± 6 months. Our meta-analysis shows that hemodynamic monitoring had no effect on all-cause mortality (HR, 0.87; 95% CI, 0.61 to 1.25; $P > 0.05$; Fig. 7). Cochran's Q value was smaller than the degrees of freedom (1 vs. 2), suggesting the true effect size was not different among the various studies. I^2 was 0%, indicating the presence of minimal heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the pooled HR (Supplementary Figure 4). Funnel plot plotting standard errors or precision against the logarithms of the hazard ratios is shown in Supplementary Figure 5 and Supplementary Figure 6, respectively. The Begg and Mazumdar rank correlation test suggested no significant publication bias (Kendal's Tau value = 0, $P > 0.05$). Egger's test demonstrated no significant asymmetry (intercept 0.69, *t* value 0.43; $P > 0.05$).

Discussion

Our study utilized both randomized clinical trial data as well as real-world observational studies to determine the utility of telemonitoring and invasive hemodynamic assessment in reducing overall mortality in HF patients. The key findings of this systematic review and meta-analysis are as follows: (1) telemonitoring significantly reduced overall mortality by 22%; (2) telemonitoring led to significant reductions in both short-term and long-term mortality; however, (3) wireless hemodynamic monitoring had no effect on mortality. Our study complements, updates, and extends previous meta-analyses published on remote patient monitoring.

Telemonitoring and Mortality

An overview of systematic reviews demonstrated reduction in mortality between 15 and 40% [53]. In 2009, Klersy and colleagues meta-analyzed 20 randomized controlled trials (RCTs) and 12 cohort studies, including 6133 patients [54]. The authors found that remote patient monitoring reduced mortality risk by 17% in RCTs, but more markedly at 47% in real-world studies. For hospitalizations, the benefit was also greater at 48% in real-world studies compared with a 7% observed in RCTs [54]. The higher reduction in mortality seen in real-world studies is a testament to the utility of close monitoring of cardiac and vital signs in patients with HF. To the best of our knowledge, this is one of the largest meta-analysis published to date, reporting on a total of 55 studies (47 RCTs and 8 cohort studies) that included 24,457 patients.

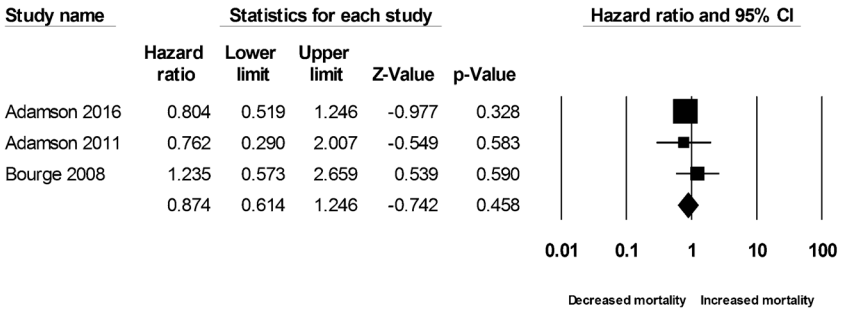

Fig. 7 Forest plot demonstrating the association between hemodynamic monitoring and mortality in heart failure

Invasive Hemodynamic Assessment and Mortality

There has been a growing interest in wireless hemodynamic monitoring using implantable devices. Currently, three devices are available for such monitoring. CardioMEMS, Chronicle, and HeartPOD measure pulmonary arterial pressure, right ventricular pressure, and left atrial pressure, respectively. A recent meta-analysis of RCTs found that hemodynamic monitoring significantly reduced all-cause and heart failure-related hospitalization events [55••]. These findings are consistent with the observations from the COMPASS-HF RCT that reported a positive association between intra-arterial pressures and the risk of hospitalization [52]. Our study complements existing meta-analytical studies by demonstrating that hemodynamic monitoring had no effect on mortality in heart failure. In terms of hemodynamic predictors, pulmonary capillary wedge pressure and right atrial pressure have been identified as strong predictors of mortality in heart failure patients [56]. The fact that no effect on mortality was noted using wireless hemodynamic devices suggests that continuous and more intense monitoring of physiological parameters do not improve mortality outcomes [57].

Comparisons of the Advantages and Disadvantages of Telemonitoring and Hemodynamic Monitoring

Interestingly, our study would suggest that telemonitoring does indeed improve survival. Other investigators have suggested that this may be due to better adherence to prescribed therapy [22]. Fundamentally, telemonitoring and hemodynamic monitoring measure different parameters, and patient participation levels or engagement may differ between the different monitoring strategies, as suggested previously [58]. For example, telemonitoring measures body weight and vital signs such as blood pressure, heart rate, and oxygen saturation. Healthcare providers can also do inquiries about symptoms such as increasing dyspnea or ankle swelling. This enables physicians to determine signs of fluid overload and guide patient management remotely. By contrast, hemodynamic monitoring measures parameters such as pulmonary arterial pressure, which is elevated in heart failure due to pulmonary vascular remodeling. In the CHAMPION trial, hemodynamic monitoring has been shown to be effective in reducing hospitalizations [49, 50], which have been linked to increased filling pressures. The fact that hemodynamic monitoring does not reduce mortality means that death in heart failure may be caused by factors other than increased pressures within the pulmonary vasculature or cardiac chambers, such as ventricular arrhythmias [59, 60]. However, the answer awaits further analysis. Moreover, hemodynamic monitoring is not without risks. Device-related or system-related complications can arise but the risks are small and the benefits are thought to outweigh the risks [48].

Results from Randomized Controlled Trials Compared with those from Observational Studies

In our meta-analysis, both RCTs and observational studies were included. Although RCTs are very well controlled and designed, they do not necessarily reflect conditions encountered in daily clinical practice. Although observational studies are susceptible to bias, confounding factors are not controlled to stringent extents that are done in RCTs. Nevertheless, we found no significant difference in mortality reduction between RCTs and cohort studies. These findings suggest that remote patient monitoring is equally effective in real-life situations.

Conclusion

This systematic review and meta-analysis shows that remote patient monitoring in heart failure by telemonitoring significantly reduces mortality rates, whereas hemodynamic monitoring had no effect on mortality.

Contributorship Statement GT: study conception and design, article screening, data extraction, manuscript drafting, and manuscript revision

MG: article screening, data extraction, quality analysis, and manuscript revision

LM: quality analysis and manuscript revision

TL: study conception and design and manuscript revision

All other authors: critically revised the manuscript for intellectual content.

All authors have approved this version of the manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

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Data Sharing

The authors welcome readers to use our meta-analytical data. Please contact the corresponding author.

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