Telemonitoring and hemodynamic monitoring to reduce hospitalization rates in heart failure: a systematic review and meta-analysis of randomized controlled trials and real-world studies

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Abstract

Background Heart failure is a significant problem leading to repeated hospitalizations. Telemonitoring and hemodynamic monitoring have demonstrated success in reducing hospitalization rates, but not all studies reported significant effects. The aim of this systematic review and meta-analysis is to examine the effectiveness of telemonitoring and wireless hemodynamic monitoring devices in reducing hospitalizations in heart failure. Methods & Results PubMed and Cochrane Library were searched up to 1st May 2017 for articles that investigated the effects of telemonitoring or hemodynamic monitoring on hospitalization rates in heart failure. In 31,501 patients (mean age: 68 ± 12 years; 61% male; follow-up 11 ± 8 months), telemonitoring reduced hospitalization rates with a HR of 0.73 (95% CI: 0.65–0.83; P < 0.0001) with significant heterogeneity (I² = 94%). These effects were observed in the short-term (≤ 6 months: HR = 0.77, 95% CI: 0.65–0.89; P < 0.01) and long-term (≥ 12 months: HR = 0.73, 95% CI: 0.62–0.87; P < 0.0001). In 4831 patients (mean age 66 ± 18 years; 66% male; follow-up 13 ± 4 months), wireless hemodynamic monitoring also reduced hospitalization rates with a HR of 0.60 (95% CI: 0.53–0.69; P < 0.001) with significant heterogeneity (I² = 64%). This reduction was observed both in the short-term (HR = 0.55, 95% CI: 0.45–0.68; P < 0.001; I² = 72%) and long-term (HR = 0.64, 95% CI: 0.57–0.72; P < 0.001; I² = 55%). Conclusions Telemonitoring and hemodynamic monitoring reduce hospitalization in both short- and long-term in heart failure patients.

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1 Introduction

Heart failure is characterized by structural abnormalities of left ventricular dysfunction and dilatation, a compensatory rise in systemic vascular resistance secondary to activation of neurohumoral pathways, inflammation, and metabolic adaptations to energy substrate utilization. It is a major public health problem globally, causing significant mortality and morbidity and placing a significant burden on healthcare systems. Hospitalization rate, a measure of healthcare resource utilization, is estimated to be 20% at one month and 50% at 6 months. A history of hospitalization is itself an independent predictor of long-term mortality. Therefore, measures to reduce hospitalization are likely beneficial in this patient population.

Telemonitoring can be used to track patients’ symptoms, adherence to medications and objective parameters such as blood pressure, heart rate, body weight and urine output. However, the effectiveness of body weight monitoring has been disputed, as the largest randomized controlled trials to date failed to demonstrate a reduction in heart failure-related hospitalizations. The reasons behind this are complex, but can be partly explained by the fact that body weight and symptoms may not provide sufficient warning of impending decompensation of cardiac function. Patient data from implantable hemodynamic monitoring studies have shown that weight is not a good measure of filling pressures that may be important determinants of decompensation. Moreover, hospitalization in heart failure may be related to not only abnormal physiological factors, but also social factors.

In addition to tele-monitoring, recent interests have focused on the roles of implantable hemodynamic monitors. Three devices, CardioMEMS, Chronicle and HeartPOD are commercially available to monitor pulmonary arterial pressure, right ventricular pressure and left atrial pressure, respectively. Several meta-analyses have been performed on remote monitoring for heart failure. For example, in 2009, the impact of remote monitoring on mortality and hospitalization rates was examined. Recently, two meta-analyses of randomized controlled trials were performed. This study complements these previous studies by providing an updated meta-analysis of both randomized controlled trials and observational studies on hospitalization rates.

2 Methods

2.1 Search strategy, inclusion and exclusion criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. It has been registered with PROSPERO (CRD42017073934). PubMed and Cochrane Library were searched up to 1st May 2017, with no language restriction, for studies that investigated the hospitalization rates in heart failure. The following search terms were used for PubMed and Cochrane Library: “tele-monitoring heart failure hospitalization” and “hemodynamic monitoring heart failure hospitalization”.

The following inclusion criteria were applied: (1) the design was a case-control, prospective or retrospective observational study or randomized controlled trial in humans; (2) patients with heart failure (both preserved and reduced ejection fraction included) were analyzed, (3) hospitalization rates, whether heart failure-specific, cardiovascular-related or all-cause, were reported or could be calculated from the published data; (3) and (4) hazard ratios (HRs) or relative risks (RRs) and their corresponding 95% CIs or data necessary to calculate these were available.

Quality assessment of case-control and cohort studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Tables 1S and 2S for telemonitoring, Tables 3S and 4S for hemodynamic monitoring), and of randomized controlled trials using the Jadad scale (Oxford quality scoring system) (Table 5S and 6S for telemonitoring and hemodynamic monitoring, respectively). The NOS evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts. This scale varied 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 (1) randomization, (2) allocation concealment, (3) double blinding and (4) withdrawal and dropouts. The total score is 7, scores 1 to 3 indicate low quality and 4 to 7 high quality.

2.2 Data extraction and statistics

Data from the different studies were entered in pre-specified spreadsheet in Microsoft Excel. All potentially relevant reports were retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. In this meta-analysis, the extracted data elements consisted of: (1) publi-
cation details: last name of first author, publication year and locations; (2) study design (cohort study or randomized controlled trial); (3) follow-up duration; (4) endpoints; (5) the quality score; and (6) the characteristics of the population including sample size, gender, age and number of subjects. Meta-analyses of observational studies are challenging due to differences in study designs and inherent biases. Two reviewers independently reviewed each included study and disagreements were resolved by adjudication with input from a third reviewer.

The endpoints for this meta-analysis were hospitalization rates. Where different types of hospitalization rates were reported, heart failure-specific rates were used preferentially, followed by cardiovascular-related hospitalization rates, and finally all-cause hospitalization rates. Multivariate adjusted hazard ratios (HRs) or relative risks (RRs) with 95% CI were extracted for each study. When values from multivariate analysis were not available, those from univariate analysis were used.

When HRs were not provided, they were calculated using raw data. The pooled adjusted risk estimates from each study as the HR values with 95% CI were presented. Different types of hospitalization rates were pooled together.

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 find the origin of the heterogeneity, sensitivity analysis excluding one study at a time did not significantly alter the pooled HR (Figure 1S). Funnel plots, Begg and Mazumdar rank correlation test and Egger’s test were used to assess for possible publication bias.

### 3 Results

Figure 1 shows a flow diagram detailing the search strategy and study selection process. For telemonitoring, a total of 120 and 111 entries were retrieved from PubMed and Cochrane Library, with 60 articles included in our final meta-analysis. For hemodynamic monitoring, a total of 220 and 53 entries were retrieved from the same databases, with 12 articles included in our final meta-analysis.

#### 3.1 Telemonitoring

For telemonitoring, a total of 31,501 patients (mean age: 68 ± 12 years old; 61% male) were included. The baseline characteristics of these studies are listed in Table 1. Six were cohort studies and 55 were randomized controlled trials. The mean follow-up duration was 11 ± 8 months. Telemonitoring reduced hospitalization rates with a HR of 0.73 (95% CI: 0.65–0.83; $P < 0.0001$, Figure 2). The Cochran’s Q value was greater than the degrees of freedom (994 vs. 59), suggesting the true effect size was different among the various studies. Moreover, $I^2$ took a value of 94%, indicating the presence of significant heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the pooled HR (Figure 1S). Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures 2S and 3S, respectively.

Figure 1. A flow diagram detailing the search strategy and study selection process for this systematic review and meta-analysis on the effects of telemonitoring and hemodynamic monitoring on hospitalization rates in heart failure.
Table 1. Characteristics of the 60 studies on telemonitoring included in this meta-analysis.

| First author / Year | Study design | Sample size (n) | Age SD % | Ejection fraction, % | Endpoints | Follow-up (months) | Variables in multivariate model |
|---------------------|-------------|----------------|----------|----------------------|-----------|--------------------|--------------------------------|
| Gallagher 2017      | RCT         | 40             | 64       | 20                   | 75        | 25                 | All-cause, HF | 1 (Univariate) |
| Sardu 2016          | RCT         | 183            | 72       | 7                    | 76        | < 35               | HF 12            | (Univariate) |
| Hale 2016           | RCT         | 25             | 72       | 11                   | 64        |                    | All-cause, HF | 3 (Univariate) |
| Ong 2016            | RCT         | 1437           | 73       | -                    | 54        | 43                 | All-cause 3, 6 | (Univariate) |
| Kraai 2016          | RCT         | 177            | 69       | 16                   | 37        | 27                 | HF 9             | (Univariate) |
| Smolis-Bąk 2015     | Cohort      | 52             | 62       | 9                    | 90        | 25                 | All-cause 18    | (Univariate) |
| Kao 2016            | Cohort      | 1246           | 78       | 12                   | 54        |                    | All-cause 36    | (Univariate) |
| Idris 2015          | RCT         | 28             | 63       | -                    | 39        | 23                 | Cardiac 3, 6   | (Univariate) |
| Pedone 2015         | RCT         | 90             | 80       | 7                    | 39        | 46                 | All-cause, HF 6 | (Univariate) |
| Bekehman 2015       | RCT         | 384            | 68       | 14                   | 97        |                    | All-cause 12    | (Univariate) |
| Vuorinen 2014       | RCT         | 94             | 58       | 17                   | 83        | 28                 | HF 6            | (Univariate) |
| Blum 2014           | RCT         | 203            | 73       | 13                   | 71        | 29                 | All-cause 48    | (Univariate) |
| Giacomelli 2014     | RCT         | 285            | 80       | -                    | 60        |                    | All-cause 9     | (Univariate) |
| Martín-Lesande 2013 | RCT         | 58             | 81       | 8                    | 59        |                    | All-cause, cause-specific 6, 12 | (Univariate) |
| Krum 2013           | RCT         | 405            | 73       | 15                   | 63        | 36                 | All-cause, HF 12 | (Univariate) |
| Sabatier 2013       | RCT         | 90             | -        | -                    | -         |                    | HF 3            | (Univariate) |
| Boyne 2012          | RCT         | 382            | 71       | 11                   | 59        | 36                 | All-cause, HF 12 | (Univariate) |
| Lyngå 2012          | RCT         | 319            | 73       | 10                   | 75        |                    | All-cause, cardiac 12 | (Univariate) |
| Seto 2012           | RCT         | 84             | 54       | 19                   | 59        | 38                 | All-cause 6     | (Univariate) |
| Dendale 2012        | RCT         | 160            | 76       | 10                   | 65        | 35                 | All-cause, HF 6 | (Univariate) |
| Koehler 2012        | RCT         | 670            | 67       | 15                   | 86        | 267                | All-cause, cardiac, HF 26 | (Univariate) |
| Kurtz 2011          | Cohort      | 138            | 68       | 17                   | 78        | 32                 | HF 12           | (Univariate) |
| Wade 2011           | RCT         | 316            | 77       | 10                   | 53        |                    | All-cause, cardiac 6 | (Univariate) |
| Domingo 2011        | RCT         | 92             | 66       | 12                   | 71        | 36                 | Cardiac excluding HF, HF 12 | (Univariate) |
| Howlett 2011        | RCT         | 122            | 67       | -                    | 65        | 46                 | All-cause 12    | (Univariate) |
| Juan 2011           | Cohort      | 120            | 76       | -                    | -         |                    | All-cause 30    | (Univariate) |
| Chaudhry 2010       | RCT         | 1653           | 61       | 16                   | 58        |                    | All-cause, HF 9 | (Univariate) |
| Antonicelli 2010    | RCT         | 57             | 78       | 7                    | 58        |                    | HF 12           | (Univariate) |
| Delaney 2010        | RCT         | 24             | 79       | 12                   | 42        |                    | All-cause, HF 3 | (Univariate) |
| Peters-Klimm 2010   | RCT         | 199            | 70       | 14                   | 72        |                    | All-cause, HF 12 | (Univariate) |
| Bowles 2009         | RCT         | 303            | 75       | 37                   | -         |                    | HF 2            | (Univariate) |
| Scherr 2009         | RCT         | 108            | 66       | 11                   | 79        | 25                 | All-cause 6     | (Univariate) |
| Mortara 2009        | RCT         | 461            | 60       | 17                   | 86        | 29                 | All-cause, HF 12 | (Univariate) |
| Dar 2009            | RCT         | 182            | 71       | 16                   | 66        |                    | All-cause, HF 6 | (Univariate) |
| Goode 2009          | RCT         | 201            | 70       | 11                   | 70        | 24                 | All-cause 16    | (Univariate) |
| Brown 2008          | RCT         | 14663          | -        | -                    | -         |                    | All-cause 12    | (Univariate) |
| Soran 2008          | RCT         | 315            | 76       | 10                   | 31        | 24                 | All-cause, HF 6 | (Univariate) |
| Antonicelli 2008    | RCT         | 57             | 78       | 10                   | 58        | 36                 | HF 12           | (Univariate) |
| Morguet 2008        | Case-control| 128            | 60       | 14                   | 88        | 44                 | All-cause, cardiac 10 | (Univariate) |

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Table 1. Cont.

| First author / Year | Study design | Sample size (n) Age SD % Male | Ejection fraction, % | Endpoints | Follow-up (months) | Variables in multivariate model |
|---------------------|--------------|-------------------------------|---------------------|-----------|-------------------|--------------------------------|
| Kashem 2008         | RCT          | 48 54 15                      | 73 26               | All-cause, HF | 12                | (Univariate)                   |
| Woodend 2008        | RCT          | 121 67 17                     | 72 -                | All-cause, HF | 3, 12             | (Univariate)                   |
| Sisk 2006           | RCT          | 406 59 19                     | 54 -                | All-cause    | 12                | (Univariate)                   |
| Riegel 2006         | RCT          | 134 72 11                     | 46 43               | All-cause    | 6                 | (Univariate)                   |
| Hudson 2005         | Cohort       | 91 74 11                       | 53 -                | All-cause    | 6                 | (Univariate)                   |
| GESICA Investigators 2005 | RCT          | 1518 65 13                    | 71 -                | All-cause, cardiac, HF | 16 | NYHA class, age, baseline treatment, comorbidity, and systolic dysfunction |
| Dunagan 2005        | RCT          | 151 - -                       | 47 -                | All-cause, HF | 12                |                               |
| Cleland et al. (2005) | RCT          | 253 67 16                     | 53 25               | All-cause, cardiac, HF | 8 |                               |
| Schofield 2005      | Cohort       | 73 67 11                       | 99 23               | All-cause    | 6                 | (Univariate)                   |
| Capomolla 2004      | RCT          | 133 57 10                     | 47 29               | All-cause, cardiac, HF | 12 | (Univariate)                   |
| Galbreath 2004      | RCT          | 1069 71 10                    | 71 54               | All-cause, HF | 6, 18             | (Univariate)                   |
| DeBusk 2004         | RCT          | 462 72 11                     | 51 -                | All-cause, cardiac, HF | 12 | (Univariate)                   |
| Roth 2004           | Cohort       | 118 74 9                      | 69 24               | All-cause    | 12                | (Univariate)                   |
| Goldberg 2003       | RCT          | 208 59 15                     | 68 <35              | All-cause, cardiac | 6 | (Univariate)                   |
| Laramee 2003        | RCT          | 287 71 12                     | 54 -                | All-cause, HF | 1.5               | (Univariate)                   |
| McDonald 2002       | RCT          | 98 71 10                      | 66 37               | HF           | 3                 | (Univariate)                   |
| Riegel 2002         | RCT          | 358 72 12                     | 49 43               | All-cause, HF | 3, 6              | (Univariate)                   |
| Kasper 2002         | RCT          | 200 62 20                     | 33 27               | HF           | 6                 | (Univariate)                   |
| Krumholz 2002       | RCT          | 88 76 13                      | 57 38               | All-cause, cardiac, HF | 12 |                               |
| Jerant 2001         | RCT          | 25 70 16                      | 48 -                | All-cause, HF | 2                 | (Univariate)                   |
| Blue 2001           | RCT          | 165 75 12                     | 58 -                | All-cause, HF | 12                | (Univariate)                   |

ACE: angiotensin converting enzyme; HF: heart failure; LV: left ventricular; NT proBNP: N-terminal pro brain natriuretic peptide; RCT: randomized controlled trial.

Begg and Mazumdar rank correlation suggested a significant publication bias (Kendal’s Tau value = −0.2, P < 0.05); Egger’s test demonstrated significant asymmetry (intercept: −1.4, t-value: 2.6; P < 0.05).

Because of the substantial heterogeneity present, we explored its possible origins. As we initially combined mortality assessed at different durations, univariate and multivariate HRs, and study design, the following subgroup analyses were performed. Firstly, we found that telemonitoring reduced hospitalization rates in the short-term (n = 27; ≤ 6 months; HR = 0.77, 95% CI: 0.65–0.89; P < 0.01; I² = 67%; Figure 4S) and long-term (n = 32; ≥ 12 months: HR = 0.73, 95% CI: 0.62–0.87; P < 0.0001; I² = 97%; Figure 5S). Secondly, subgroup analysis was performed for the type of HR. Meta-analysis of univariate HRs produced a pooled effect estimate of 0.91 (95% CI: 0.84–0.99; P < 0.05) whilst reducing I² to 71%. Thirdly, subgroup analysis was performed for study design. Meta-analysis of randomized controlled trials (RCTs) yielded a pooled effect estimate of 0.96 (95% CI: 0.95–0.97; P < 0.0001) whilst reducing I² to 72%. By contrast, meta-analysis of cohort studies yielded a significantly lower HR of 0.38 (95% CI: 0.36–0.41; P < 0.0001) whilst preserving I² at 94%. Together, these findings suggest the duration over which mortality was assessed, type of HRs and study design to be possible sources of heterogeneity.

3.2 Hemodynamic monitoring

For wireless hemodynamic monitoring, a total of 4831 patients were included. The baseline characteristics of these studies are listed in Table 2. Four publications were cohort studies and eight publications were based on data from three randomized controlled trials (CHAMPION, COMPASS-HF, ...
Figure 2. Pooled hazard ratios for studies examining the effects of telemonitoring on hospitalization rates in heart failure.

The mean follow-up duration was 13 ± 4 months. The mean age was 66 ± 18 years) of whom 66% were male. Wireless hemodynamic monitoring significantly reduced hospitalization rates with a HR of 0.60 (95% CI: 0.53–0.69; \( P < 0.001 \)). The Cochran’s Q value was greater than the degrees of freedom (36 vs. 13), suggesting the true effect size was different among the various studies. \( I^2 \) took a value of 64%, indicating the presence of significant heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the pooled HR (Figure 6S). Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures 7S and 8S, respectively. Begg and Mazumdar rank correlation suggested a significant publication bias (Kendal’s Tau value = 0.5, \( P < 0.05 \)). Egger’s test demonstrated significant asymmetry (intercept: \(-2.2\), t-value = 3.2; \( P < 0.01 \)).
Table 2. Characteristics of the 12 studies on hemodynamic monitoring included in this meta-analysis.

| First author/Year | Study design | Population | Type of hemodynamic monitoring | Sample size (n) | Age, yrs SD | % Male | Ejection fraction, % | Endpoints | Follow-up (months) | Variables in multivariate model |
|-------------------|--------------|------------|--------------------------------|----------------|-------------|--------|---------------------|-----------|-----------------|-------------------------------|
| Desai 2017 | Cohort | HF | Pulmonary arterial pressure | 1114 | 71 11 64 | - | All-cause, HF | 6 | (Univariate) |
| Jermyn 2016 | Cohort | HF | Pulmonary arterial pressure | 77 | - - | - | HF | 12 | (Univariate) |
| Adamson 2016 | RCT | HF | Pulmonary arterial pressure | 245 | 73 8 | - | HF | 17 | (Univariate) |
| Abraham 2016 | RCT | HF | Pulmonary arterial pressure | 347 | 62 18 | - | All-cause, HF | 17 | (Univariate) |
| Raina 2015 | RCT | HF | Pulmonary arterial pressure | 537 | 62 18 | - | HF | 18 | (Univariate) |
| Adamson 2014 | RCT | HF with preserved ejection fraction | Pulmonary arterial pressure | 119 | 66 12 60 51 | HF | 18 | (Univariate) |
| | | HF with reduced ejection fraction | | 66 | 60 13 76 | 23 | 18 | (Univariate) |
| Benza 2015 | RCT | HF with pulmonary hypertension | Pulmonary arterial pressure | 314 | 62 13 72 | - | HF | 15 | (Univariate) |
| | | HF without pulmonary hypertension | | 236 | 61 13 74 | - | HF | 15 | (Univariate) |
| Adamson 2011 | RCT | HF | Right ventricular pressure | 400 | 55 21 34 | 23 | All-cause, HF | 12 | (Univariate) |
| Abraham 2011 | RCT | HF | Pulmonary arterial pressure | 550 | 62 18 73 | 60 | HF | 6 | (Univariate) |
| Ritzema 2010 | Cohort | HF | Left atrial pressure | 40 | 66 10 78 | 32 | Combined HF hospitalization and all-cause mortality | 3 | (Univariate) |
| Bourge 2008 | RCT | HF | Right ventricular pressure | 274 | 58 19 65 | 33 | HF | 6 | (Univariate) |
| Adamson 2003 | Cohort | HF | Right ventricular pressure | 32 | 59 10 38 | 29 | HF | 17 | (Univariate) |

HF: heart failure; RCT: randomized controlled trial.

Significant reductions in hospitalization rates were observed in both short-term (HR: 0.55, 95% CI: 0.45–0.68; \( P < 0.001; I^2 = 72\%; Figure 9S) and long-term (HR: 0.64, 95% CI: 0.57–0.72; \( P < 0.001; I^2 = 55\%; Figure 10S) For the different types of hemodynamic devices, hospitalization rates were significantly reduced using pulmonary pressure monitoring (HR: 0.58, 95% CI: 0.50–0.66; \( P < 0.001; I^2 = 67\%; Figure 11S) or left atrial pressure monitoring (HR: 0.16, 95% CI: 0.04–0.68; \( P < 0.05\). It was not possible to perform a meta-analysis for left atrial pressure monitoring because this was only assessed by one study. Right ventricular pressure monitoring tended to reduce hospitalization...
rates (HR: 0.69, 95% CI: 0.47–1.01; $\hat{F} = 61\%$; Supplementary Figure 12S) but this did not reach statistical significance ($P = 0.058$).

4 Discussion

This is a systematic review and meta-analysis of randomized controlled trials and real-world studies on the effects of remote patient monitoring on hospitalization rates in heart failure, complementing previous meta-analyses.\[11–13\] The main findings are the following: (1) hospitalization rates can be reduced by remote patient monitoring using either telemonitoring or hemodynamic monitoring by 26% (95% CI: 17%–35%) and 40% (95% CI: 31%–47%), respectively; (2) telemonitoring reduced hospitalization rates by 24% in the short-term (≤ 6 months) and 27% in the long-term (≥ 12 months); and (3) hemodynamic monitoring reduced hospitalization rates by 45% in the short-term and 37% in the long-term.

Telemonitoring is a broad term referring to the making telephone contact with patients to enquire about symptoms, adherence to pharmacotherapy, and obtain information on clinically important parameters such as heart rate, blood pressure, body weight and urine output. This in turn enables appropriate advice to be offered to patients.\[17\] The benefits of home monitoring systems on hospitalization are possibly due to its good potential for detecting early signs of decompensation and reinforcement of patient’s self-care education, and are especially useful for those who needs extra support, such as older and more frail patients.\[87,88\] Telemonitoring appears to have limited potential in early detection of worsening heart failure, but most effective when patient education toward medical adherence and patient self-care efficacy are reinforced. These different effects of telemonitoring could be attributable to the wide distribution or the disparate outcome of the effects on hospitalization, and to the heterogeneity observed. There are different vital signs that could be used to provide a warning for heart failure decompensation. These are heart rate, heart rate variability,\[89\] blood pressure, body weight and urine output.\[6,89–91\] For example, increases in body weight can predict acute decompensation requiring hospitalization.\[91\] However, a study found that diastolic blood pressure, systolic blood pressure x heart rate and diastolic blood pressure x heart rate, but not heart rate or systolic blood pressure by itself, predicted 3-month major adverse cardiac events.\[90\]

Hemodynamic monitoring refers to the continuous measurement of cardiac chamber or vascular pressures. Three devices are available: CardioMEMS (pulmonary arterial pressure),\[92\] Chronicle (right ventricular pressure)\[93\] and HeartPOD (left atrial pressure).\[94\] The rationale behind hemodynamic monitoring is that increases in intracardiac and pulmonary arterial pressures were detectable several weeks prior to worsening of clinical symptoms and signs.\[4,9\] Subgroup analyses were performed for the different hemodynamic parameter measured. The evidence for pulmonary artery pressure monitoring is the strongest, with a 42% reduction in hospitalization rates. Right ventricular pressure monitoring tended to reduce hospitalization rates by around 31% but this was not statistically significant. It was not possible to perform a meta-analysis for left atrial monitoring, as only one study has been published to date. Nevertheless The LAPTOP-HF trial is currently ongoing and when completed will provide important data for determining whether left atrial monitoring will similarly reduce hospitalization rates in heart failure.\[95\]

Theoretically, hemodynamic monitoring should reduce hospitalization rates to greater extents than usual care or telemonitoring if patients were offered appropriate advice to mitigate abnormal cardiac physiology, such as fluid overload or bradycardia, by altering medication regimens at home so that hospitalization would not be necessary. Our meta-analysis found that the risk reduction for hospitalization using hemodynamic monitoring was slightly higher at 40% compared to 27% using telemonitoring, but this was not significantly different. This meta-analysis provides data that less-invasive remote monitoring by telemedicine is equally effective as more invasive forms of hemodynamic monitoring. The former approach may be more cost-effective and yet able to prevent hospitalizations. Therefore, healthcare resources can be focused on the patients who do require hospital admission, who can be offered additional investigations such as quantification of blood biomarkers and echocardiography for guiding their management.\[96,97\]

4.1 Limitations

There are some limitations of this study that must be recognized. Firstly, we had observed a substantial heterogeneity for the HRs for the effects of telemonitoring on hospitalization rates. In our study, hazard ratios of randomized controlled trials and cohort studies, which are different study designs, were initially pooled together. A recent Cochrane review showed that there were no significant difference in the effective estimates between observational studies and randomized controlled trials, suggesting that factors other than study design are responsible for differences in outcomes.\[98\] However, in our subgroup analysis, we found that the pooled HR was significantly lower for cohort studies when compared to the HR for RCT. Therefore, meta-analysis should combine the effect estimates
separately based on trial design. Moreover, this subgroup analysis resulted in a reduction of $F$ to 72% for RCTs, suggesting that this contributed to the heterogeneity observed. Other sources, as assessed by our subgroup analyses, were the duration over which mortality was assessed (short-term versus long-term mortality) and whether the HRs were univariate or multivariate HRs. Secondly, we detected significant bias using both Begg and Mazumdar rank correlation test and Egger’s test, in that the reported HRs skewed towards reduced hospitalization by telemonitoring. In other words, fewer HRs were from the studies reporting a lack of effect on hospitalization. Therefore, this may represent publication bias in which only positive findings were published by the journals, with negative results possibly not published. Thirdly, there were only four cohort studies that assessed hemodynamic monitoring. As only three RCTs with a limited number of subjects were conducted, future RCTs are needed for different types of hemodynamic monitoring systems, especially left atrial pressure monitoring, for which the HR was only available in one study and it was therefore not possible to conduct a subgroup analysis for this system. Finally, there is a lack of studies that directly compare hemodynamic monitoring to telemonitoring, which needs to be investigated in the future, especially given the invasive nature of hemodynamic monitoring systems.

4.2 Conclusions

This meta-analysis demonstrates that both telemonitoring and hemodynamic monitoring are equally effective approaches to reduce hospitalization rates in heart failure. Telemonitoring should be used more widely, since it is less invasive than hemodynamic monitoring and may be more cost-effective. However, direct comparisons between these modes of monitoring are needed in the future.

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| Number | First Author | Selection (score) | Comparability (score) | Total Score |
|--------|--------------|-------------------|-----------------------|-------------|
|        |              | Case definition   | Representativeness of cases |               |             |
|        |              |                    | Selections of controls | Definition of controls |       |
|        |              | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method ascertainment participants | Nonresponse rate |
| 1      | Morguet 2008 | -                  | 1                     | 1           | 1           | 6          |

Table 2S. Quality ratings for included cohort studies using the Newcastle-Ottawa quality assessment scale for telemonitoring.

| Number | First Author | Selection (score) | Comparability (score) | Total Score |
|--------|--------------|-------------------|-----------------------|-------------|
|        |              | Representative of exposed cohort | Selections of non-exposed cohort | Assessment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Ascertainment of outcome | Was follow-up long enough for outcomes to occur? | Adequacy of follow up of cohorts |             |
| 1      | Kao 2016     | 1                  | 1                    | 0            | 0            | 1           | 1           | 1           | 9          |
| 2      | Smolis-Bąk 2015 | 1                  | 1                    | 1            | 1            | 2 (age, comorbidities) | 1           | 1           | 1          |
| 3      | Kurtz 2011   | 1                  | 1                    | 1            | 1            | 2 (age, LVEF)    | 1           | 1           | 9          |
| 4      | Hudson 2005  | 1                  | 0                    | 1            | 1            | 0            | 1           | 1           | 1          |
| 5      | Schofield 2005 | 1                  | 1                    | 1            | 1            | 2            | 1           | 1           | 9          |
| 6      | Roth 2004    | 1                  | 1                    | 1            | 1            | 2            | -           | 1           | 8          |

LVEF: left ventricular ejection fraction.

Table 3S. Quality ratings for included case-control studies using the Newcastle-Ottawa quality assessment scale for hemodynamic monitoring.

| Number | First Author | Selection (score) | Comparability (score) | Total Score |
|--------|--------------|-------------------|-----------------------|-------------|
|        |              | Case definition   | Representativeness of cases |               |             |
|        |              |                    | Selections of controls | Definition of controls |       |
|        |              | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method ascertainment participants | Nonresponse rate |
| 1      | Jermyn 2016 | 1                  | 1                    | 1            | 2           | 1           | 1           | 1           | 8          |
| 2      | Abraham 2016 | 1                  | 1                    | 1            | 1            | 2           | 1           | 1           | 9          |
| 3      | Raina 2015   | 1                  | 1                    | 1            | 2           | 1           | 1           | 1           | 8          |
| 4      | Benza 2015   | 1                  | 1                    | 1            | 2           | 1           | 1           | 1           | 8          |
| 5      | Abraham 2011 | 1                  | 1                    | 1            | 2           | 1           | 1           | 1           | 9          |

Table 4S. Quality ratings for included cohort studies using the Newcastle-Ottawa quality assessment scale for hemodynamic monitoring.

| Number | First Author | Selection (score) | Comparability (score) | Total Score |
|--------|--------------|-------------------|-----------------------|-------------|
|        |              | Representative of exposed cohort | Selections of non-exposed cohort | Assessment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Ascertainment of outcome | Was follow-up long enough for outcomes to occur? | Adequacy of follow up of cohorts |             |
| 1      | Desai 2017   | 1                  | 1                    | 1            | 1            | 2           | 1           | 1           | 1          |
| 2      | Ritzema 2010 | -                  | 1                    | 1            | 2            | 1           | 1           | 1           | 8          |
| 3      | Adamson 2003 | 1                  | 1                    | 1            | 2            | 1           | 1           | 1           | 9          |
Table 5S. Quality ratings for included randomized controlled trials using the Jadad quality assessment scale for telemonitoring.

| Number | Study                  | Randomization | Allocation concealment | Double blinding | Withdrawals and dropouts | Total score |
|--------|------------------------|---------------|------------------------|-----------------|---------------------------|-------------|
| 1      | Gallagher 2017         | 2             | 1                      | 1               | 1                         | 5           |
| 2      | Sardu 2016             | 2             | 2                      | 2               | 0                         | 6           |
| 3      | Hale 2016              | 1             | 0                      | 0               | 1                         | 2           |
| 4      | Ong 2016               | 2             | 2                      | 2               | 1                         | 7           |
| 5      | Kraai 2016             | 2             | 1                      | 1               | 1                         | 5           |
| 6      | Idris 2015             | 1             | 0                      | 0               | 1                         | 2           |
| 7      | Pedone 2015            | 1             | 1                      | 2               | 1                         | 5           |
| 8      | Bekelman 2015          | 2             | 0                      | 0               | 1                         | 3           |
| 9      | Vuorinen 2014          | 1             | 0                      | 0               | 1                         | 2           |
| 10     | Blum 2014              | 1             | 0                      | 0               | 1                         | 2           |
| 11     | Giacomelli 2014        | 1             | 0                      | 0               | 1                         | 2           |
| 12     | Martin-Lesende 2013    | 2             | 0                      | 1               | 1                         | 4           |
| 13     | Krum 2013              | 1             | 1                      | 1               | 1                         | 4           |
| 14     | Sabatier 2013          | 1             | 0                      | 0               | 1                         | 2           |
| 15     | Boyne 2012             | 2             | 0                      | 2               | 1                         | 5           |
| 16     | Lyngaå 2012            | 1             | 1                      | 2               | 1                         | 5           |
| 17     | Seto 2012              | 2             | 2                      | 2               | 1                         | 7           |
| 18     | Dendale 2012           | 2             | 2                      | 2               | 1                         | 7           |
| 19     | Koehler 2012           | 2             | 1                      | 1               | 1                         | 5           |
| 20     | Wade 2011              | 1             | 0                      | 0               | 1                         | 2           |
| 21     | Domingo 2011           | 1             | 0                      | 0               | 1                         | 2           |
| 22     | Howlett 2011           | 1             | 0                      | 0               | 1                         | 2           |
| 23     | Chaudhry 2010          | 2             | 2                      | 2               | 1                         | 7           |
| 24     | Antonicelli 2010       | 1             | 0                      | 0               | 1                         | 2           |
| 25     | Delaney 2010           | 1             | 0                      | 0               | 1                         | 2           |
| 26     | Peters-Klinn 2010      | 2             | 2                      | 2               | 1                         | 7           |
| 27     | Bowles 2009            | 1             | 2                      | 2               | 1                         | 6           |
| 28     | Scherr 2009            | 1             | 0                      | 2               | 1                         | 4           |
| 29     | Mortara 2009           | 2             | 2                      | 2               | 1                         | 7           |
| 30     | Dar 2009               | 2             | 1                      | 2               | 1                         | 6           |
| 31     | Goode 2009             | 1             | 0                      | 0               | 1                         | 2           |
| 32     | Brown 2008             | 2             | 1                      | 0               | 1                         | 4           |
| 33     | Soran 2008             | 1             | 1                      | 2               | 1                         | 5           |
| 34     | Antonicelli 2008       | 1             | 0                      | 0               | 1                         | 2           |
| 35     | Kashem 2008            | 2             | 0                      | 0               | 1                         | 3           |
| 36     | Woodend 2008           | 1             | 0                      | 0               | 1                         | 2           |
| 37     | Sisk 2006              | 2             | 2                      | 2               | 1                         | 7           |
| 38     | Riegel 2006            | 1             | 0                      | 0               | 1                         | 2           |
| 39     | GESICA Investigators 2005 | 1       | 0                      | 0               | 1                         | 2           |
| 40     | Dunagan 2005           | 2             | 0                      | 0               | 1                         | 3           |
| 41     | Cleland 2005           | 1             | 1                      | 2               | 1                         | 5           |
| 42     | Capomolla 2004         | 1             | 0                      | 0               | 1                         | 2           |
| 43     | Galbreath 2004         | 1             | 0                      | 0               | 1                         | 2           |
| 44     | DeBusk 2004            | 2             | 1                      | 1               | 1                         | 5           |
| 45     | Goldberg 2003         | 1             | 0                      | 0               | 1                         | 2           |
| 46     | Laramee 2003           | 2             | 1                      | 2               | 1                         | 6           |
| 47     | McDonald 2002         | 1             | 1                      | 2               | 1                         | 5           |
| 48     | Riegel 2002           | 1             | 2                      | 2               | 1                         | 6           |
| 49     | Kasper 2002           | 1             | 0                      | 1               | 1                         | 3           |
| 50     | Krumholz 2002         | 1             | 0                      | 0               | 1                         | 2           |
| 51     | Jerant 2001           | 2             | 2                      | 0               | 1                         | 5           |
| 52     | Blue 2001             | 1             | 1                      | 1               | 1                         | 4           |
### Table 6S. Quality ratings for included randomized controlled trials using the Jadad quality assessment scale for hemodynamic monitoring.

| Number | Study         | Randomization | Allocation concealment | Double blinding | Withdrawals and dropouts | Total score |
|--------|---------------|---------------|------------------------|-----------------|--------------------------|-------------|
| 1      | Adamson 2016  | 1             | 1                      | 1               | 1                        | 4           |
| 2      | Adamson 2014  | 1             | 1                      | 1               | 1                        | 4           |
| 3      | Adamson 2011  | 1             | 1                      | 1               | 1                        | 4           |
| 4      | Bourge 2008   | 1             | 1                      | 2               | 1                        | 5           |

### Figure 1S. Sensitivity analysis for hazard ratio on hospitalizations using telemonitoring.

- **Decreased hospitalization**
- **Increased hospitalization**
Figure 2S. Funnel plot of standard error against the logarithm of hazard ratio for hospitalizations using telemonitoring.

Figure 3S. Funnel plot of precision against the logarithm of hazard ratio for hospitalizations using telemonitoring.

Study name | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
--- | --- | --- | --- | --- | --- |
Gallagher 2017 | 1.670 | 0.459 | 6.070 | 0.779 | 0.436 |
Hale 2016 | 0.310 | 0.040 | 2.401 | -1.121 | 0.262 |
Ong 2016 | 1.030 | 0.882 | 1.203 | 0.374 | 0.709 |
Ibris 2015 | 1.000 | 0.814 | 1.228 | 0.000 | 1.000 |
Pedone 2015 | 0.370 | 0.181 | 0.755 | -2.731 | 0.006 |
Vuorinen 2014 | 0.810 | 0.525 | 1.249 | -0.954 | 0.340 |
Martim-Lesende 2013 | 0.800 | 0.413 | 1.549 | -0.662 | 0.506 |
Sabatier 2013 | 0.500 | 0.289 | 0.866 | -2.473 | 0.013 |
Seto 2012 | 0.850 | 0.716 | 1.034 | -1.508 | 0.128 |
Dendale 2012 | 0.570 | 0.359 | 0.906 | -2.376 | 0.017 |
Wade 2011 | 1.190 | 0.718 | 1.874 | 0.606 | 0.544 |
Delaney 2010 | 0.670 | 0.133 | 3.376 | -0.485 | 0.632 |
Bowles 2009 | 2.200 | 0.915 | 5.288 | 1.762 | 0.078 |
Scherr 2009 | 0.530 | 0.271 | 1.036 | -1.859 | 0.063 |
Dar 2009 | 1.380 | 0.775 | 2.457 | 1.065 | 0.274 |
Soran 2008 | 0.710 | 0.430 | 1.171 | -1.341 | 0.180 |
Woodruff 2008 | 0.410 | 0.317 | 1.365 | -0.325 | 0.746 |
Riegel 2006 | 0.910 | 0.544 | 1.522 | -0.360 | 0.719 |
Hudson 2005 | 0.610 | 0.463 | 0.804 | -3.501 | 0.000 |
Holmfield 2005 | 0.150 | 0.075 | 0.300 | -5.964 | 0.000 |
Galbraith 2004 | 1.140 | 0.726 | 1.790 | 0.569 | 0.569 |
Golding 2003 | 0.730 | 0.350 | 1.521 | -0.840 | 0.401 |
Laramee 2003 | 0.820 | 0.460 | 1.461 | -0.674 | 0.501 |
McDonald 2002 | 0.080 | 0.010 | 0.680 | -2.399 | 0.016 |
Riegel 2002 | 0.510 | 0.351 | 0.742 | -3.525 | 0.000 |
Kasper 2002 | 0.980 | 0.701 | 1.371 | -0.118 | 0.906 |
Jennet 2001 | 0.230 | 0.039 | 1.777 | -1.409 | 0.159 |

Figure 4S. Subgroup analysis for hazard ratio on short-term hospitalizations using telemonitoring.
Figure 5S. Subgroup analysis for hazard ratio on long-term hospitalizations using telemonitoring.

Figure 6S. Sensitivity analysis for hazard ratio on hospitalizations using hemodynamic monitoring.
Figure 7S. Funnel plot of standard error against the logarithm of hazard ratio for hospitalizations using hemodynamic monitoring.

Figure 8S. Funnel plot of precision against the logarithm of hazard ratio for hospitalizations using hemodynamic monitoring.

Figure 9S. Subgroup analysis for hazard ratio on short-term hospitalizations using hemodynamic monitoring.
### Figure 10S. Subgroup analysis for hazard ratio on long-term hospitalizations using hemodynamic monitoring.

| Study name   | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|--------------|--------------|-------------|-------------|---------|---------|
| Desai 2017   | 0.660        | 0.572       | 0.762       | -5.662  | 0.000   |
| Adamson 2016 | 0.510        | 0.371       | 0.701       | -4.140  | 0.000   |
| Abraham 2016 | 0.670        | 0.556       | 0.808       | -4.190  | 0.000   |
| Rainer 2015  | 0.580        | 0.284       | 1.186       | -1.493  | 0.135   |
| Adamson 2014 (HFpEF) | 0.300 | 0.184       | 0.490       | -4.812  | 0.000   |
| Adamson 2014 (HFpEF) | 0.740 | 0.623       | 0.880       | -3.416  | 0.000   |
| Benza 2015 (HFpPHC) | 0.640 | 0.508       | 0.807       | -3.782  | 0.000   |
| Benza 2015 (HFpPHC) | 0.600 | 0.407       | 0.884       | -2.584  | 0.010   |
| Adamson 2011  | 0.905        | 0.702       | 1.166       | -0.774  | 0.439   |
| Abraham 2011 | 0.630        | 0.518       | 0.767       | -4.614  | 0.000   |
| Adamson 2003  | 0.440        | 0.230       | 0.841       | -2.484  | 0.013   |
|              | 0.636        | 0.565       | 0.717       | -7.443  | 0.000   |

### Figure 11S. Subgroup analysis for hazard ratio on long-term hospitalizations using pulmonary pressure monitoring.

| Study name   | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|--------------|--------------|-------------|-------------|---------|---------|
| Desai 2017   | 0.550        | 0.493       | 0.614       | -10.698 | 0.000   |
| Jermyn 2016  | 0.160        | 0.068       | 0.386       | -4.073  | 0.000   |
| Adamson 2016 | 0.510        | 0.371       | 0.701       | -4.140  | 0.000   |
| Abraham 2016 | 0.670        | 0.556       | 0.808       | -4.190  | 0.000   |
| Rainer 2015  | 0.580        | 0.284       | 1.186       | -1.493  | 0.135   |
| Adamson 2014 (HFpEF) | 0.300 | 0.184       | 0.490       | -4.812  | 0.000   |
| Adamson 2014 (HFpEF) | 0.740 | 0.623       | 0.880       | -3.416  | 0.001   |
| Benza 2015 (HFpPHC) | 0.640 | 0.508       | 0.807       | -3.782  | 0.000   |
| Benza 2015 (HFpPHC) | 0.600 | 0.407       | 0.884       | -2.584  | 0.010   |
| Abraham 2011 | 0.630        | 0.518       | 0.767       | -4.614  | 0.000   |
|              | 0.576        | 0.500       | 0.664       | -7.601  | 0.000   |

### Figure 12S. Subgroup analysis for hazard ratio on long-term hospitalizations using right ventricular pressure monitoring.

| Study name   | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|--------------|--------------|-------------|-------------|---------|---------|
| Adamson 2011 | 0.905        | 0.702       | 1.166       | -0.774  | 0.439   |
| Bourge 2008  | 0.640        | 0.423       | 0.968       | -2.116  | 0.034   |
| Adamson 2003 | 0.440        | 0.230       | 0.841       | -2.484  | 0.013   |
|              | 0.689        | 0.469       | 1.012       | -1.897  | 0.058   |