Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 18, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.08.017

A Meta-Analysis of Remote Monitoring of Heart Failure Patients

Catherine Klersy, MD, MSc,* Annalisa De Silvestri, MSc,* Gabriella Gabutti, MA,†
François Regoli, MD,*‡ Angelo Auricchio, MD‡

Pavia, Italy; and Lugano, Switzerland

Objectives The purpose of this study was to assess the effect of remote patient monitoring (RPM) on the outcome of chronic heart failure (HF) patients.

Background RPM via regularly scheduled structured telephone contact between patients and health care providers or electronic transfer of physiological data using remote access technology via remote external, wearable, or implantable electronic devices is a growing modality to manage patients with chronic HF.

Methods After a review of the literature published between January 2000 and October 2008 on a multidisciplinary heart failure approach by either usual care (in-person visit) or RPM, 96 full-text articles were retrieved: 20 articles reporting randomized controlled trials (RCTs) and 12 reporting cohort studies qualified for a meta-analysis.

Results Respectively, 6,258 patients and 2,354 patients were included in RCTs and cohort studies. Median follow-up duration was 6 months for RCTs and 12 months for cohort studies. Both RCTs and cohort studies showed that RPM was associated with a significantly lower number of deaths (RCTs: relative risk [RR]: 0.83, 95% confidence interval [CI]: 0.73 to 0.95, $p = 0.006$; cohort studies: RR: 0.53, 95% CI: 0.29 to 0.96, $p < 0.001$) and hospitalizations (RCTs: RR: 0.93, 95% CI: 0.87 to 0.99, $p = 0.030$; cohort studies: RR: 0.52, 95% CI: 0.28 to 0.96, $p < 0.001$). The decrease in events was greater in cohort studies than in RCTs.

Conclusions RPM confers a significant protective clinical effect in patients with chronic HF compared with usual care. (J Am Coll Cardiol 2009;54:1683–94) © 2009 by the American College of Cardiology Foundation

Patients with chronic heart failure (HF) frequently experience repeated hospitalizations that are not only a result of progression of underlying disease but more often due to poor adherence to drug therapy, inadequate drug therapy, changes in diet, poor self-care, and inadequate patient support. Approximately 70% of all direct and indirect costs generated by HF patients are due to hospitalization (1). Recent guidelines of both European and American scientific societies recommended a multidisciplinary care approach that coordinates care along the continuum of HF and throughout the chain of care delivery by various services within the health care systems (1,2)

From the *Service of Biometry and Clinical Epidemiology and †Scientific Documentation Center, Scientific Direction Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; and the ‡Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland. Dr. Klersy is a consultant to Boston Scientific and Medtronic. Dr. De Silvestri is a consultant to Boston Scientific. Dr. Gabutti is a consultant to Boston Scientific. Dr. Auricchio is a consultant to Philips, Medtronic, Biotronik GmbH, and Sorin and has received speaker fees from GE Healthcare, Philips, Medtronic, Biotronik GmbH, and Sorin.

Manuscript received May 25, 2009; revised manuscript received August 31, 2009, accepted August 31, 2009.

The multidisciplinary HF care approach is implemented by in-person follow-up visits and is regarded as usual care of HF patients. More recently, alternative approaches have been proposed including regularly scheduled structured telephone contact between patients and health care providers and electronic transfer of physiological data using remote access technology via external, wearable, or implantable electronic devices. This latter approach allows frequent or continuous assessment of some physiological parameters related to HF exacerbation, and such technology-based monitoring is the base for early detection of HF worsening, thus permitting remote disease management (1).

Results of some randomized controlled trials (RCTs) (3–22) and several observational studies (23–34) support the hypothesis that the multidisciplinary care approach or the management strategy of structured communication with the health care provider may reduce both the incidence of hospitalizations and death and eventually related costs with respect to more traditional follow-up of patients with chronic HF. Moreover, recent systematic reviews and meta-analyses provided further evidence in favor of implementation of telemonitoring in chronic HF patients (35–38). Of note, guidelines recommend remote monitoring of symp-

Abbreviations and Acronyms

CI = confidence interval

HF = heart failure

RCT = randomized controlled trial

RPM = remote patient monitoring

RR = relative risk

toms (including drug adverse effects) and signs of HF (Class I recommendation, Level of Evidence: C) (1). Since the last review by Clark et al. (35), which exclusively included RCTs and all published articles until mid-2006, several observational studies and RCTs have become available (6,9,10,21).

To update earlier systematic reviews, we conducted a literature search including both RCTs and observational studies and performed a meta-analysis of the use of telemonitoring in chronic HF and its related outcomes compared with usual care of HF patients.

Methods

Bibliographic search. The National Guideline Clearinghouse, PubMed, EMBASE, Cinhail, and the Cochrane Library databases were searched throughout October 2008 using the following search criteria: 1) full-text articles in peer-reviewed journals published between January 2000 and October 2008 in which at least 2 treatment arms were evaluated (thus uncontrolled studies were excluded); 2) RCTs or observational cohort (C) studies; and 3) language of publication could be English, Spanish, German, French, or Italian (Table 1). A total of 253 abstracts were retrieved; however, 56 studies were excluded because they were simultaneously present in more than 1 database; thus, 197 abstracts were finally collected and reviewed.

Data extraction. For each article, we collected the following information: type of study (multicenter or single center), total number of patients included in the trial, number of arms/periods, mean duration of follow-up, age, sex, New York Heart Association functional class, and left ventricular ejection fraction of included patients and for each arm, person-years of follow-up, and the modality of care. Three different approaches of care were identified: 1) a usual care approach, which referred to in-person visits at the doctor's office, at a multidisciplinary outpatient clinic, or at emergency department without additional phone calls to and from the patient; 2) a telephone monitoring approach including regularly scheduled structured telephone contact between patients and health care providers (with or without home visits) and reporting of symptoms and/or physiological data; and 3) a technology-assisted monitoring approach relying on information communication technology, with transfer of physiological data collected via remote (at the patient's home) external monitors or via cardiovascular

Table 1 Bibliographic Search Strategy

Database	Access Date	Search Strategy	No. of Articles Found
National Guideline Clearinghouse	July 2, 2008	Heart failure remote monitoring	13
	October 23, 2008	Heart failure remote monitoring	0
PubMed	July 4, 2008	("Heart Failure"[Mesh] AND "Telemedicine"[Mesh]) OR ("heart failure" AND "remote patient monitoring") Limits: Published from January 1, 2000, to July 4, 2008 English, French, German, Italian, Spanish	99
	October 23, 2008	[("Heart Failure"[Mesh] AND "Telemedicine"[Mesh]) OR ("heart failure" AND "remote patient monitoring")] AND (2008/07/03:2008/10/23[mhda] OR 2008/07/03:2008/10/23[edat]) Limits: Published from January 1, 2000, to July 4, 2008 English, French, German, Italian, Spanish	7
EMBASE	July 4th, 2008	[("heart failure"/exp AND "telemedicine"/exp AND [embase]/lim AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) AND [2000-2008]/py)] OR ["heart failure"/exp AND "remote patient monitoring" AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) AND [embase]/lim AND [2000-2008]/py)]	75
	October 23, 2008	[("heart failure"/exp AND "telemedicine"/exp AND [embase]/lim AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) AND [2008]/py)] OR ["heart failure"/exp AND "remote patient monitoring" AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) AND [embase]/lim AND [2008]/py)]	11
Cinhail	July 4, 2008	Heart failure AND (telemedicine OR remote patient monitoring) Limits: Published from January 2000 to July 2008 Language: English, French, German, Italian, Spanish	38
	October 23, 2008	Heart failure AND (telemedicine OR remote patient monitoring) Limits: Published from July 2000 to October 2008 English, French, German, Italian, Spanish	0
Cochrane Library	July 4, 2008	(heart failure):ti, from 2000 to 2008 in Cochrane Reviews	10
	October 23, 2008	(heart failure):ti, in 2008 in Cochrane Reviews	0*

*Number of new reviews from July 4 to October 23, 2008.

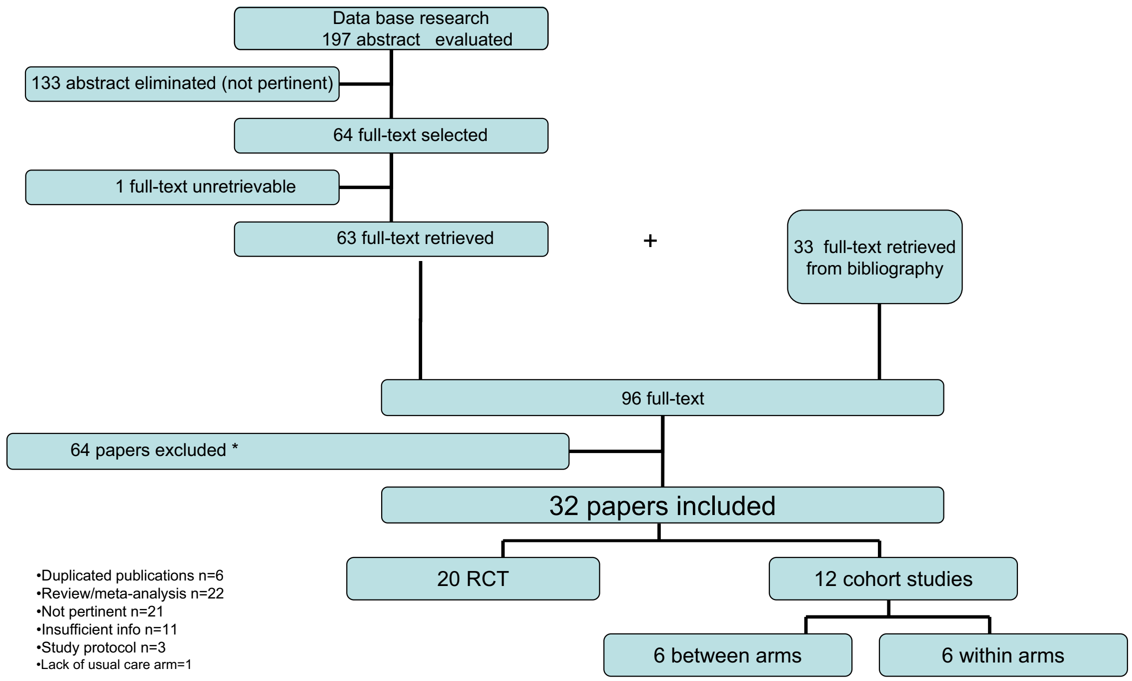

Figure 1 **Study Flow Chart Displaying Study Disposition**

RCT = randomized controlled trial.

implantable electronic devices. Finally, the latter 2 approaches were collectively considered and identified as remote patient monitoring (RPM).

For each of these approaches, great attention was paid to retrieval of information about clinical and cardiovascular parameters monitored such as symptoms, body weight, blood pressure, electrocardiogram, heart rate, arrhythmias, shock device, heart rate variability, activity log, oxygen saturation, and right ventricular pressures.

The following outcomes were considered: death from any cause, first hospitalization for any cause and first hospitalization for HF, and a combined end point of first hospitalization or death from any cause. Only a few articles reported the cause-specific mortality, and, thus, this was not included.

Two authors (C.K. and A.D.S.) reviewed all abstracts and selected articles to ensure that they met the inclusion criteria. Each of them separately extracted the information from the articles, and whenever a discrepancy was noted, it was reconciled by consensus. The quality of the study was rated based on adherence to the CONSORT and STROBE statements and graded on a 0 to 10 visual analog scale.

Meta-analysis. The primary end point of the study was the comparison of the cumulative incidence of events (number of patients with events/total number of patients per arm) between the usual care approach and RPM strategies (telephone and technology-assisted monitoring approaches) for each of the outcomes considered (death from any cause, first hospitalization for any cause, and hospitalization for HF), as well as for the combined outcome of first hospitalization or death from any cause. Death and hospitalization from any cause were assessed separately for RCTs and cohort (between) studies, whereas hospitalization for HF could be assessed for RCTs only. A secondary analysis of the primary end point comparing incidence rates of events (number of events/total person time per arm) gave similar results (data not shown).

To assess the stability of our conclusions, we performed a series of sensitivity analyses: 1) comparison of the cumulative incidence of events with the usual care approach with that of the telephone monitoring and the technology-assisted monitoring approach; 2) comparison of the cumulative incidence of events with the usual care approach with that of the RPM approach, according to duration of follow-up ($\leq$6 and $>$6 months) and study quality ($<$8 and $\geq$8 on a visual analog scale).

The relative risk (RR) and 95% confidence interval (CI) for each outcome in each study were calculated. Study RRs were then pooled according to the Mantel-Haenszel fixed-effects method. To better account for differences among studies, we also fitted DerSimonian and Laird random-effects models. Statistical heterogeneity was evaluated by the Cochran Q test and measured by the I^2 statistic. When the I^2 statistic was $>$20%, we considered the random-effects RR to be preferable. The presence of severe publication and

JACC Vol. 54, No. 18, 2009
October 27, 2009:1683–94

Table 2 Study Design and Population: Summary

Characteristic	RCT (n = 20)	Cohort Study (n = 20)
Year of publication		
2001	3	0
2002	4	0
2003	2	1
2004	2	2
2005	3	4
2006	2	2
2007	0	2
2008	4	1
Multicenter study, n (%)	9 (45)	2 (17)
Parallel group design, n (%)	20 (100)	6 (50)
No. of patients		
Total	6,258	2,354
Median over study	182	123
25th to 75th percentiles	100–382	73–354
Range	34–1,518	24–502
Sex distribution,* n (%)		
Male	3,995 (64)	1,163 (60)
Female	2,263 (36)	765 (40)
Study mean age distribution, yrs		
Median over study	70	66
25th to 75th percentiles	63–72	60–74
Range	54–78	59–81
Left ventricular ejection fraction, %†		
Median over study	35	40
25th to 75th percentiles	25–38	35–44
Range	22–43	35–44
NYHA functional class III to IV,‡ n (%)	3,306 (54)	480 (83)
Study mean follow-up duration, months		
Median over study	6	12
25th to 75th percentiles	4–12	8–12
Range	2–18	2–17
Study mean follow-up duration (months), categorized, n (%)		
0–3	5 (25)	1 (8)
3–6	6 (30)	1 (8)
6–12	7 (35)	9 (75)
12–18	2 (10)	1 (8)
Study quality rating, n (%)		
<8	10 (50)	10 (83)
≥8	10 (50)	2 (17)

*In one observational study, sex distribution was not provided; thus, the sum of the number of male and female subjects enrolled is less than the total number of subjects. †Left ventricular ejection fraction available in 9 RCTs and 3 cohort studies. ‡NYHA functional class available in 18 RCTs and 3 cohort studies.

NYHA = New York Heart Association; RCT = randomized controlled trial.

other biases, for each outcome, was excluded by funnel plots (Online Appendix).

Stata version 10.1 (Stata Corp., College Station, Texas) was used for computation.

Results

Identification of articles. Sixty-three full-text articles were retrieved from 197 abstracts; an additional 33 full-text articles were identified from references in the articles retrieved; thus, a total of 96 full-text articles were collected. However, 64 of them were excluded for 1 or more of the following reasons: duplicate publication, review or meta-analysis, lack of pertinence, study protocol, insufficient information provided, or lack of a usual care arm (Fig. 1). They are listed in the Online Appendix together with the reason for exclusion. Thus, 20 RCTs (3–22) and 12 cohort studies (23–34) were available. Six cohort studies had a between-arm and 6 had a within-arm (before-after) design.

Study population. As shown in Table 2, RCTs were evenly distributed over the 9 years of literature reviewed, and 4 of them were published in 2008. Results of cohort studies started to be published only in the year 2001. A limited proportion of studies (45% of RCTs and 17% of cohort studies) had been conducted at multiple centers.

A total of 6,258 patients were enrolled in RCTs and 2,354 patients in cohort studies. Women were well represented (36% and 40% of the study population for RCTs and cohort studies, respectively). The median age over studies was 70 years in RCTs and 66 years in cohort studies. Median left ventricular ejection fraction was 35% in RCTs and 40% in cohort studies. Fifty-four percent of patients in RCTs were of New York Heart Association functional class III to IV compared with 83% of patients in cohort studies. However, left ventricular ejection fraction and New York Heart Association functional class were only very partially retrievable and thus are to be interpreted with caution.

Median follow-up duration was 6 months, and approximately 25% of the follow-up was 3 months or less in RCTs. In contrast, median follow-up duration was 12 months in cohort studies; only 1 study had a follow-up of 3 months or less. One-half of the RCTs had a high-quality scoring (≥8) compared with only 17% of cohort studies.

RPM approach (telephone and technology-assisted monitoring). Among the RCTs, 2 studies (3,5) compared 3 strategies (usual care, telephone monitoring, and technology-assisted monitoring), whereas the remaining 18

Table 3 Pattern of Follow-Up and Monitoring Approach in the 32 Studies Included

Pattern of Follow-Up	RCT*	Cohort Study
Usual care†	20	12
Family physician	10	2
Home care service	2	1
Cardiologist	4	0
Not specified	9	9
Telephone-monitoring approach	13	0
Phone call	12	—
Phone call + home visit	1	—
Technology-assisted approach	9	12
Home-monitoring equipment	6	11
Implantable device	1	1
Phone call with decision support system	2	0

*The total number of RCTs is 20, with a total number of RPM arms of 22 (2 studies with 2 RPM arms each). †Multiple choices allowed.

RCT = randomized controlled trial.

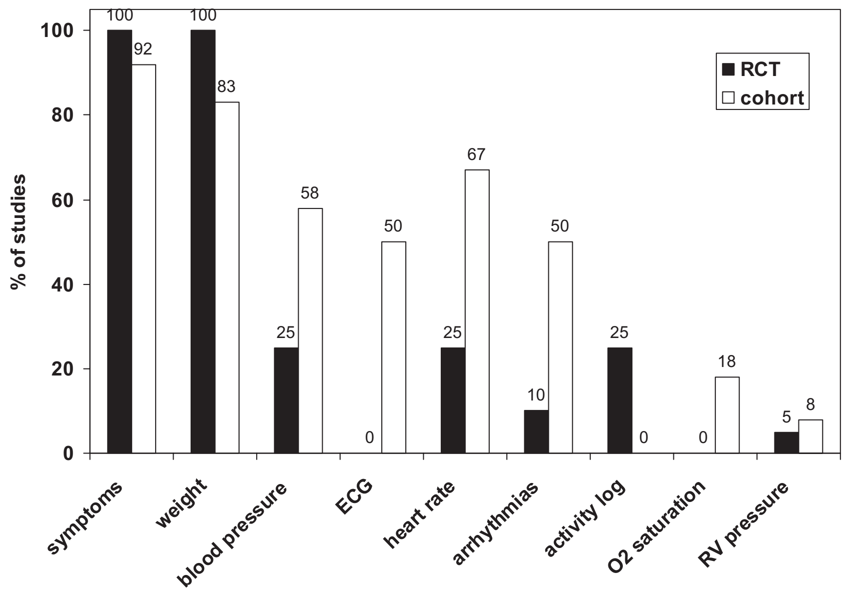

Figure 2 **Parameters Monitored in RCTs and Cohort Studies**

ECG = electrocardiogram; RCT = randomized controlled trial; RV = right ventricular.

Table 4 **Study Outcome Summary: Event Incidence (Incidence Rate) and 95% Confidence Interval**

Study Outcome	RPM	N_{tot}	N_{ev}	PY	Cumulative Incidence, % (95% CI)	Incidence Rate per 100 PY (95% CI)
RCT						
Death	No	2,813	397	2,675.2	14.1 (12.8–15.4)	14.8 (13.5–16.4)
	Yes	3,320	390	3,321.9	11.7 (10.7–12.9)	11.7 (10.7–13.0)
	Telephone monitoring	2,598	312	2,934.5	12.0 (10.8–13.3)	10.6 (9.5–11.9)
	Technology assisted	722	78	387.4	10.8 (8.6–13.3)	20.1 (15.9–2.1)
Patients hospitalized	No	1,985	901	1,915.1	45.4 (43.2–47.6)	47.0 (44.0–50.2)
	Yes	2,137	918	2,035.8	43.0 (40.8–45.1)	45.1 (42.2–48.1)
	Telephone monitoring	1,662	670	1,752.9	40.3 (37.9–42.7)	38.2 (37.9–42.7)
	Technology assisted	475	248	282.9	52.2 (47.6–56.8)	87.6 (0.77–0.99)
Patients hospitalized for HF	No	2,079	546	1,986.4	26.3 (24.4–28.2)	27.4 (25.2–29.9)
	Yes	2,231	424	2,103.4	19.0 (17.4–20.7)	20.2 (18.3–22.2)
	Telephone monitoring	1,735	302	1,828.2	17.4 (15.6–19.3)	16.5 (14.7–18.5)
	Technology assisted	496	122	275.2	24.6 (20.9–28.6)	45.4 (43.2–47.6)
Combined end point	No	1,090	553	1,279.1	50.7 (47.7–53.7)	43.2 (39.7–47.0)
	Yes	1,348	608	1,452.1	38.9 (30.7–35.1)	41.9 (38.6–45.3)
	Telephone monitoring	1,185	525	1,343.4	44.3 (41.4–47.1)	39.1 (35.8–42.6)
	Technology assisted	163	83	108.7	50.9 (43.0–58.8)	76.4 (60.8–94.7)
Cohort (between)						
Death	No	945	123	808.2	13.0 (10.9–15.3)	15.2 (12.6–18.1)
	Yes	980	67	839.7	6.8 (5.3–8.6)	8.0 (6.2–10.1)
Patients hospitalized	No	399	153	331.3	38.3 (33.5–43.3)	46.2 (39.1–54.1)
	Yes	420	84	348.8	20.0 (16.3–24.1)	24.1 (19.2–29.8)
Patients hospitalized for HF	No	124*	48	72.3	38.7 (30.1–47.9)	66.4 (49.0–88.0)
	Yes	158*	19	92.2	12.0 (7.4–18.1)	20.6 (12.4–32.2)
Combined end point	No	96*	15	80.0	15.6 (9.0–24.4)	18.7 (10.5–30.1)
	Yes	32*	3	26.7	9.4 (2.0–25.0)	11.2 (2.3–32.8)

*Single study; in cohort study, RPM is always technology assisted.

CI = confidence interval; HF = heart failure; N_{ev} = number of patients with event/number of events; N_{tot} = total number of patients; Pts = patients; PY = person-years (= mean follow-up per arm in months × number of patients per arm/12); RPM = remote patient monitoring.

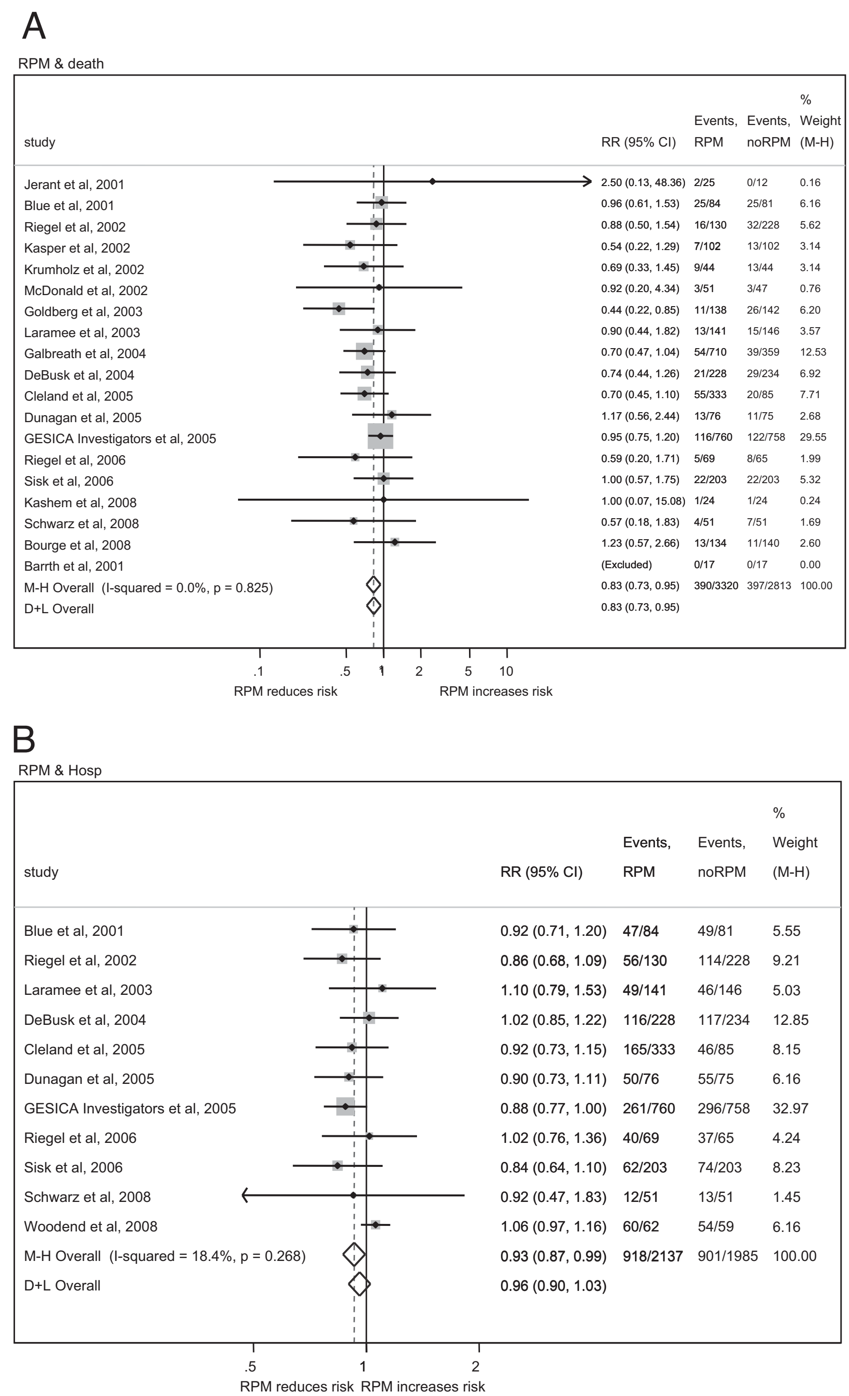

Figure 3 **Forrest Plots for the Analysis of the Primary End Point**

(A) Association of remote patient monitoring (RPM) and death. **(B)** Association of RPM and hospitalization. *Continued on next page.*

studies (4,6–22) compared the usual care approach with the telephone-monitoring approach (11 studies) or technology-assisted monitoring approach (7 studies). In contrast, in all cohort studies, the usual care approach was always compared with the technology-assisted monitoring approach. Detailed methodology of care in the analyzed studies is given in Table 3. Of note, in 9 of 20 RCTs and in 9 of 12 cohort studies, the modality for performing usual care was not provided.

In RCTs, symptoms and body weight were always recorded. In a similar manner, symptoms and body weight were monitored in nearly all cohort studies (11 of 12 studies

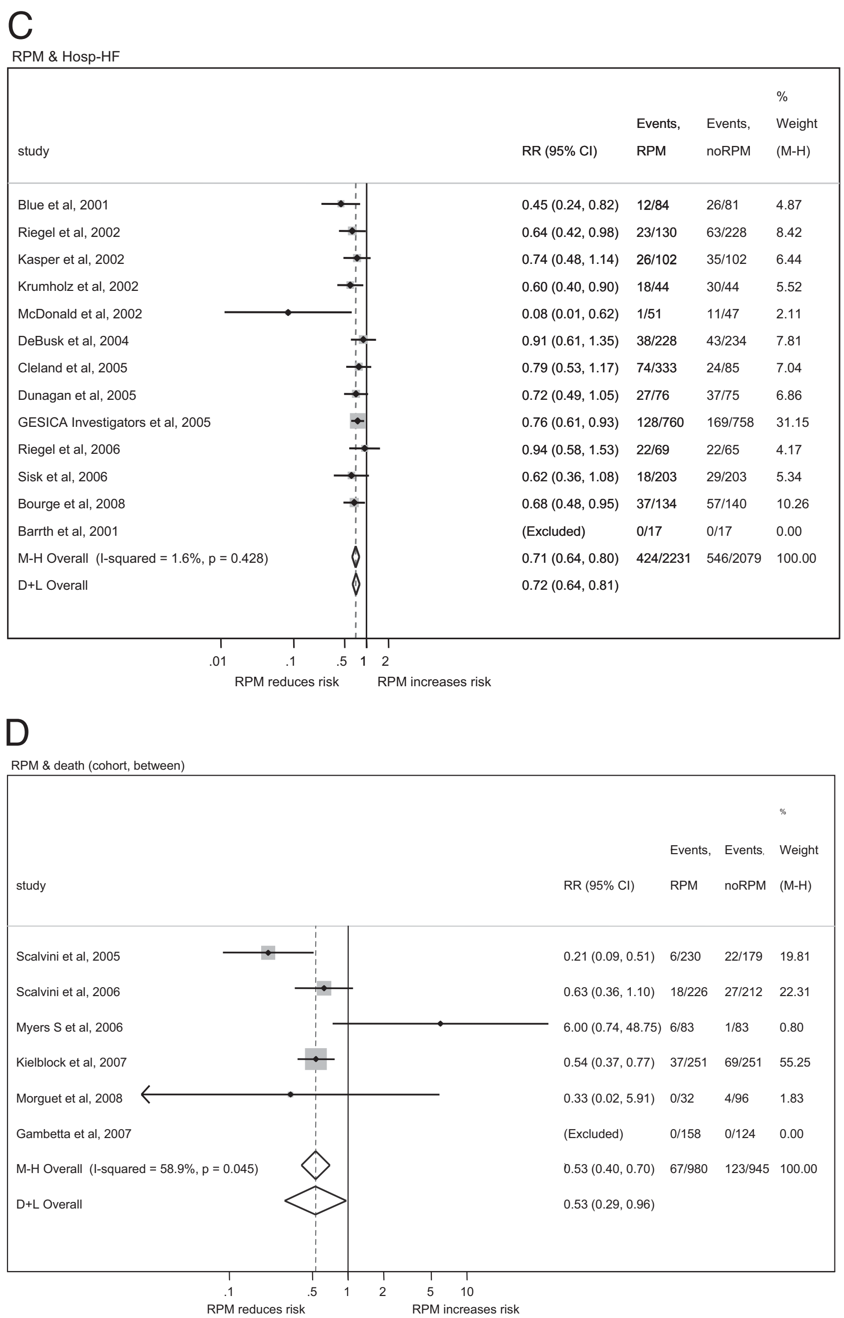

Figure 3 **Continued**

(C) Association of RPM and hospitalization for heart failure. **(D)** Association of RPM and the combined end point of death and first hospitalization. The **vertical line** corresponds to a relative risk (RR) of 1 (no effect); RRs to the **left** indicate that RPM reduces risk; RRs to the **right** indicate that RPM increases risk. The pooled estimates are indicated by a **diamond** (fixed effects above; random effects below). CI = confidence interval; D+L = DerSimoniam and Laird random-effects method; M-H = Mantel and Haenszel fixed-effects method.

and 10 of 12 studies, respectively). Blood pressure, patient physical activity, and heart rate were monitored in a limited number of RCTs (5 of 20 studies); in contrast, blood pressure and heart rate were monitored twice as frequently in cohort studies than in RCTs (7 of 12 studies and 8 of 12 studies, respectively). All other cardiovascular parameters were monitored anecdotally (1 to 2 studies each), as detailed in Figure 2.

Incidence rates of events. Table 4 shows the study outcomes for both RCTs and cohort (between) studies in terms of cumulative incidence and incidence rates per 100 person-years, together with their 95% CIs for each of the relevant

JACC Vol. 54, No. 18, 2009
October 27, 2009:1683–94

outcomes and for each care approach. Table 4 also reports the total number of patients, the total number of patients with events, and the person-years of observation.

In the cohort studies with a before-after design, the incidence rate of hospitalization was calculated over 4 studies and equaled 86.4 (95% CI: 75.7 to 98.3) in the study period with the usual care approach and 21.1 per 100 person-years (95% CI: 16.0 to 27.4) in the study period with the RPM approach. The incidence rate of hospitalization for HF was calculated over 2 studies and equaled 100% (95% CI: 98% to 100%) in the study period with the usual care approach and 28.4 per 100 person-years (95% CI: 21.1 to 37.3) in the study period with the RPM approach. Overall, the incidence of death, hospitalization for all causes, hospitalization for HF, or combined death and hospitalization was lower with the RPM compared with the usual care approach.

Outcomes in RCTs. The association of the RPM approach with death, hospitalization, hospitalization for HF, and the combined outcome of death and hospitalization is shown in Figure 3 and summarized in Table 5.

RPM was associated with a significantly lower number of deaths (RR: 0.83, 95% CI: 0.73 to 0.95, $p = 0.006$) compared with usual care (Fig. 3A). No heterogeneity between studies was shown ($p = 0.82$). A similar, yet less important, protective effect was found comparing RPM with usual care when hospitalization was considered (RR: 0.93, 95% CI: 0.87 to 0.99, $p = 0.030$); the higher heterogeneity (18.4%, $p = 0.27$) resulted in a loss of statistical significance when considering the random-effects RR (Fig. 3B). The strongest protective effect of RPM compared with usual care was found when hospitalization for HF was analyzed (RR: 0.71, 95% CI: 0.64 to 0.80, $p < 0.001$) with little heterogeneity between studies (Fig. 3C). The combined end point of death and first hospitalization (available in a few studies) gave comparable results (RR: 0.86, 95% CI: 0.79 to 0.94, $p < 0.001$). Some heterogeneity was present (28%, $p = 0.22$), although without loss of significance in the random-effects model (Fig. 3D).

In a sensitivity analysis, the telephone or technology-assisted monitoring approach provided an equally large benefit compared with usual care for almost every outcome. Of note, the protective effect on death of the technology-assisted approach was slightly greater than that provided by the structured telephone approach (Table 5). Moreover, when RRs were computed separately according to duration of follow-up (short/long) and to quality of study (low/high), the association between RPM and death or RPM and hospitalization for HF was maintained (Table 5).

Outcomes in cohort studies. Figure 4 shows the effect of RPM on death and hospitalization. RPM was associated with a significantly lower number of deaths (random-effects RR: 0.53, 95% CI: 0.29 to 0.96, $p < 0.001$) and hospitalizations (random-effects RR: 0.52, 95% CI: 0.28 to 0.96, $p < 0.001$) compared with usual care. High heterogeneity between studies was shown ($I^2 = 59\%$ for death and $I^2 = 82\%$ for hospitalization) (Figs. 4A and 4B).

Discussion

This meta-analysis showed that RPM significantly reduced the risk of death, hospitalization for any cause, and hospitalization for HF compared with usual care in RCTs. The reduction in risk of death and hospitalization was even more pronounced when meta-analyzing cohort studies.

Our analysis confirms, extends, and updates previous systematic reviews (35–38). To the best of our knowledge, this represents the largest number of meta-analyzed patients. A previously published analysis (35) included 14 RCTs (all published before May 2006) and totaled 4,369 patients; in contrast, our analysis included 20 RCTs (all published before October 2008) and reported on 6,133 patients, which represents 1,764 patients or 40.3% more patients than the most recent meta-analysis of RCTs by Clark et al. (35). Since the publication of that meta-analysis, 5 additional RCTs were published, including 4 in 2008 (6,9,10,21); moreover, nearly all cohort studies included in our meta-analysis were published in the past 5 years. That clearly indicates a growing interest in RPM in the cardiology community; a similarly great interest in telemedicine is also found at the highest European institutional level, which recently urged health care systems across Europe to embrace the technology. There are, however, technological and organizational challenges for health care systems that are expected to increase in view of the aging population in Western countries and the increase in the prevalence of HF in the general population worldwide. Which parameters to monitor, how to monitor them most efficiently, and how to organize the response of the health care professionals to data obtained from monitoring to optimize patient care are all questions that need to be answered.

In contrast to most previous reviews and meta-analyses, our study included both RCTs and cohort studies. RCTs are very accurate in their design but may not reflect real life well enough, which, in contrast, is probably better represented in cohort studies; conversely, cohort studies often do not sufficiently control for confounding factors. The fact that the use of RPM in cohort studies led to a reduction of both mortality and hospitalization, which was of similar magnitude or even greater than that observed in RCTs, may be considered a confirmation of the value of the technology as such. This observation also emphasizes the importance of including in meta-analyses both RTCs and cohort studies. There are additional differences between this meta-analysis and most of the previous meta-analyses; indeed, our meta-analysis and that of Clark et al. (35) considered only those studies in which RPM was compared with usual care. These criteria are more stringent than those of other meta-analyses (36–38), which included different multidisciplinary approaches. The beneficial effect of RPM on mortality and hospitalization observed in our meta-analysis was consistent with that reported by Clark et al. (35) (Table 6), who, however,

Table 5 Meta-Analysis of the Selected Outcomes

	Death		Patients Hospitalized		Patients Hospitalized HF		Combined	
End Point	**n***	**RR (95% CI)**	**n***	**RR (95% CI)**	**n***	**RR (95% CI)**	**n***	**RR (95% CI)**
Primary end point								
RPM vs. usual care	18		11		12		6	
Fixed		0.83 (0.73–0.95)		0.93 (0.87–0.99)		0.71 (0.63–0.80)		0.86 (0.79–0.94)
Random		0.84 (0.73–0.95)		0.96 (0.90–1.03)		0.72 (0.64–0.81)		0.85 (0.77–0.95)
Heterogeneity (I^2 and p)		0%		18%		2%		28%
Sensitivity analyses								
Telephone monitoring vs. usual care	12		7		9		6	
Fixed		0.86 (0.74–0.99)		0.92 (0.85–0.99)		0.70 (0.62–0.80)		0.86 (0.79–0.94)
Random		0.86 (0.74–0.99)		0.92 (0.85–0.99)		0.70 (0.60–0.82)		0.86 (0.77–0.95)
Heterogeneity (I^2)		0%		0%		14%		31%
Technology-assisted vs. usual care	7		5		4		1	
Fixed		0.72 (0.55–0.95)		0.94 (0.84–1.06)		0.74 (0.61–0.91)		
Random		0.73 (0.55–0.96)		0.97 (0.85–1.12)		0.75 (0.61–0.92)		
Heterogeneity (I^2)		0%		44%		0%		
RPM vs. usual care if FU ≤6 months	9		5		5		1	
Fixed		0.74 (0.56–0.97)		0.98 (0.87–1.11)		0.68 (0.55–0.83)		
Random		0.74 (0.56–0.98)		1.02 (0.94–1.12)		0.70 (0.54–0.92)		
Heterogeneity (I^2)		0%		6%		35%		
RPM vs. usual care if FU >6 months	9		6		7		5	
Fixed		0.86 (0.74–1.00)		0.91 (0.84–0.98)		0.73 (0.64–0.83)		0.87 (0.80–0.95)
Random		0.86 (0.74–1.00)		0.91 (0.84–0.99)		0.72 (0.63–0.83)		0.87 (0.80–0.94)
Heterogeneity (I^2)		0%		0%		0%		0%
RPM vs. usual care if quality <8	8		3		3		1	
Fixed		0.70 (0.54–0.90)		1.06 (0.91–1.24)		0.63 (0.49–0.82)		
Random		0.70 (0.54–0.90)		1.06 (0.97–1.15)		0.63 (0.39–1.03)		
Heterogeneity (I^2)		0%		0%		56%		
RPM vs. usual care if quality ≥8	10		8		9		5	
Fixed		0.89 (0.76–1.04)		0.91 (0.84–0.98)		0.73 (0.64–0.83)		0.87 (0.80–0.95)
Random		0.89 (0.76–1.03)		0.91 (0.85–0.98)		0.73 (0.64–0.82)		0.87 (0.80–0.94)
Heterogeneity (I^2)		0%		0%		0%		0%

*n = number of studies.
FU = follow-up; RR = relative risk; other abbreviations as in Table 4.

focused their analysis on RCTs. Some difficulty may exist in comparing the results of our meta-analysis with those of a previous review of cohort studies by Gonseth et al. (36). They included cohort studies that were published before 2004 and summarized the data of comprehensive disease management programs and very little, if any, of technology-assisted RPM. Telemonitoring technology has substantially changed over the past years and has moved from structured phone contact to more automatic external, wearable, or implantable devices (21,31,39). In addition, modern technology relies more and more on central servers, sophisticated algorithms for automatic review of transmitted data and alerts, expert systems for direct interaction with either the patient or health care provider, and dedicated online health care providers and in-hospital remote device and disease management units (39,40).

Although well-designed cohort studies may be as accurate as RCTs (41,42), they should be considered with caution because they often do not sufficiently control for confounding factors, thus resulting in high estimates of risk. As a matter of fact, the estimates of the pooled risk reduction of death and hospitalization in the cohort studies in our meta-analysis were unadjusted for confounding, which resulted in an almost 50% risk reduction compared with at best 20% in the RCTs (Table 6). Moreover, only a few cohort studies satisfied our inclusion criteria, leading to wide CIs for the estimates of RR. An additional caveat exists regarding the interpretation of observational studies included in this meta-analysis because enrollment in the RPM arm was voluntary; this might bias the results toward a high adherence to the monitoring program given the high level of motivation of these patients and resulting in a lower incidence of events. Moreover, clinical, social, and/or demographic factors may be considered additional confounders and should be adjusted for in any analysis. All these reasons emphasize the difficulty in stating a difference in effect size between RCTs and cohort studies. It is important to note that same drawbacks apply to a previous meta-analysis and explain the similar large differences observed between estimates of risk reduction in RCTs and cohort studies (36). Future cohort studies should be designed to assess the role of RPM in large populations having as end

JACC Vol. 54, No. 18, 2009
October 27, 2009:1683–94

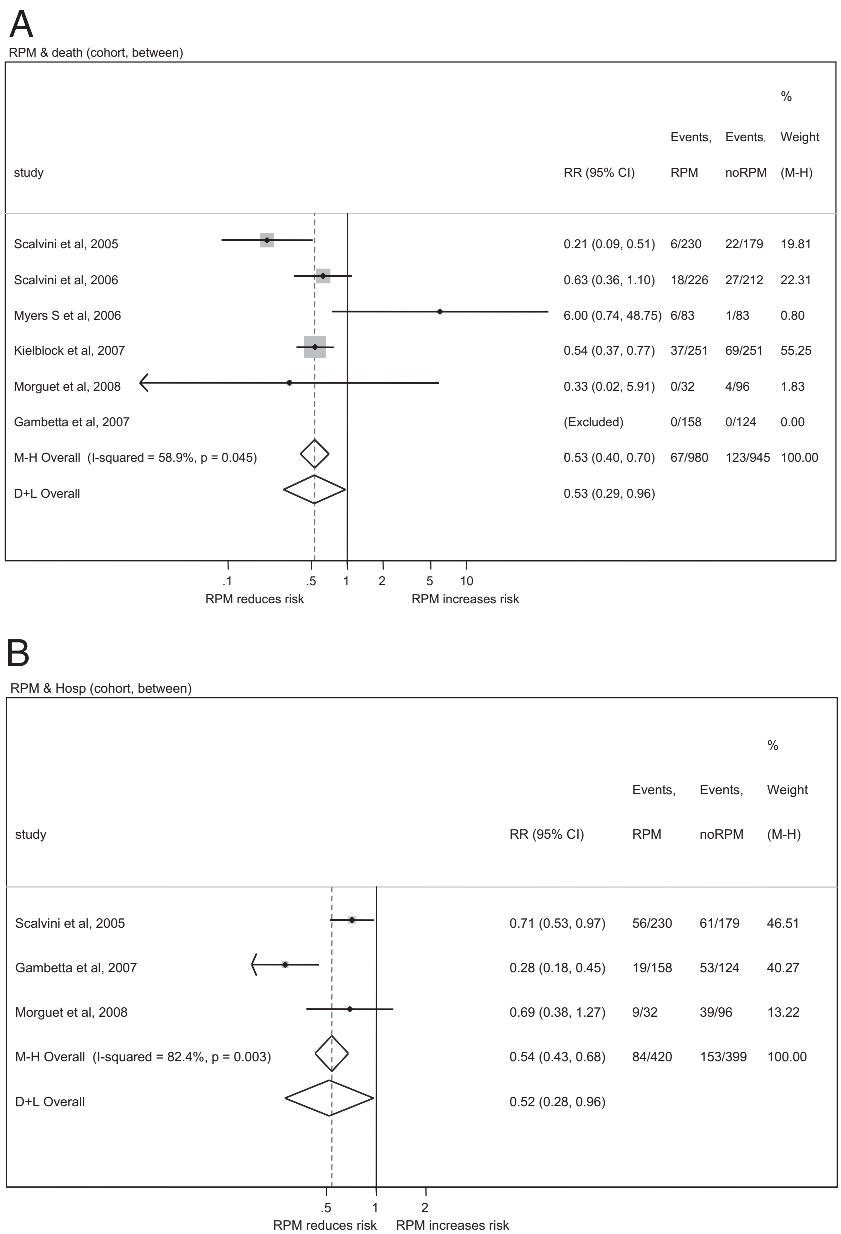

Figure 4 **Forrest Plots for the Analysis of the Primary End Point in a Between-Arm Design Cohort**

(A) Association of RPM and death. **(B)** Association of RPM and hospitalization. See Figure 3 for explanation.

points death and hospitalization (any cause and HF) while accounting for the underlying patients' characteristics.

Because RPM exclusively collects symptom and physiological data related to HF, a greater effect on death or hospitalization from HF rather than on death or hospitalization from any cause was expected. In keeping with the stated hypothesis, the protective effect of RPM on hospitalization for HF was greater than on hospitalizations for any cause. The reduction in hospitalization for HF (−7%) was similar to that found in the Clark et al. (35) meta-analysis (−5%) and was statistically significant in our meta-analysis due to the larger sample size. Unfortunately, only hospitalizations for HF could be meta-analyzed here, given the scarce information on cause of death in the selected articles. However, RPM also showed a significant protective effect on death from any cause in our review; usually elderly patients would have comorbidities, and some of these may have been exacerbated by their cardiac condition. Thus, better follow-up and care for the latter might have also increased their overall well-being and survival.

Particular care was taken to evaluate the robustness of our results in a series of sensitivity analyses. We did not observe major differences in risk reduction when analyzing sepa-

Table 6 Comparison of Our Results With Selected Published Meta-Analyses

Study	Gonseth et al. (36), 2004		McAlister et al. (37), 2004	Roccaforte et al. (38), 2005	Clark et al. (35), 2007	Current study, 2009	
Study Type	RCT	Cohort	RCT	RCT	RCT	RCT	Cohort
No. of studies	27	27	29	33	14	20	12 (6 between)
Years for database search	1966–2003		1966–2003	1993–2004	2002–2006	2000–2008	
Death	*	*					
No. of studies	10	2	22	28	14	19	6
No. of patients	2,985	440	3,781	5,308	4,349	6,133	1,925
RR (95% CI)	0.82 (0.72–0.94)	0.37 (0.24–0.58)	0.83 (0.70–0.99)	0.84 (0.74–0.94)	0.80 (0.69–0.92)	0.83 (0.73–0.95)	0.53 (0.29–0.96)
Hospitalization							
No. of studies	16	8	23	32	8	11	8
No. of patients	4,440	1,599	4,313	7,387	3,641	4,122	819
RR (95% CI)	0.88 (0.79–0.97)	0.50 (0.34–0.74)	0.84 (0.75–0.93)	0.86 (0.82–0.91)	0.95 (0.89–1.02)	0.93 (0.87–0.99)	0.52 (0.28–0.96)
Hospitalization for HF							
No. of studies	11	5	19	20	9	13	N/A
No. of patients	3,160	1,875	3,008	3,817	3,429	4,310	
RR (95% CI)	0.70 (0.62–0.79)	0.38 (0.16–0.93)	0.73 (0.66–0.82)	0.69 (0.63–0.77)	0.79 (0.69–0.89)	0.71 (0.64–0.80)	
Comments	DMP pooled; same conclusions with sensitivity analyses (DMP modality and follow-up); includes control visits; no control for confounders in cohort studies		Different DMP with different effectiveness; no effect on mortality if only telephone + referral to family physician (but 95% CI width comparable to other modes)	Different DMP equally effective; same conclusions with sensitivity analyses (DMP modality; little description of usual care)	Structured telephone support (symptoms only) and telemonitoring (symptoms and physiological data): different effectiveness	Same conclusions with sensitivity analyses (type of RPM, follow-up, study quality); technology- and nontechnology-assisted RPM equally effective; no control for confounders in cohort studies	

*Combined end point of death and hospitalization.
DMP = disease management program; N/A = not available; other abbreviations as in Table 4.

rately follow-up of ≤6 and >6 months and high- or low-quality of the study. Similarly, risk reduction was consistent for all outcomes when evaluating separately the telephone and technology-assisted approach, despite these 2 approaches being inherently different. This is in line with the results of the only 2 available articles that directly compared these 2 modalities (3,5). Similar results were reported by Gonseth et al. (36) and Roccaforte et al. (38), whereas others have reported that regularly scheduled structured telephone contact, referral to a family physician (36–38), and monitoring of symptoms alone (35) were less effective in reducing risk than more comprehensive monitoring approaches (Table 6).

The heterogeneity of RCTs was small in this review and lower than that reported by Roccaforte et al. (38) (40% to 50%), but comparable to that reported by Clark et al. (35). One possible explanation for this discrepancy may reside in the fact that Clark et al. (35) considered older studies, a more general intervention pattern, and possibly the fact that the usual care arm included a large variety of situations. Much greater heterogeneity was observed for cohort studies (50%), although this was less than the heterogeneity reported by Gonseth et al. (36) (60% to 85%); this might be due to both the lack of control of confounders and the selection bias in the enrollment process of either arms.

Conclusions

The results of this meta-analysis support the benefit of RPM on mortality and hospitalization rates. This benefit was present in both RCTs and cohort studies. This analysis provides further support for the recent recommendation by European and American scientific societies. Mid- and long-term cost-effectiveness of remote patient monitoring, however, remains to be evaluated.

Reprint requests and correspondence: Dr. Catherine Klersy, Servizio di Biometria ed Epidemiologia Clinica, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy. E-mail: klersy@smatteo.pv.it.

REFERENCES

1. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388–442.
2. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.
3. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH, TEN-HMS Investigators. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. J Am Coll Cardiol 2005;45:1654–64.

4. Dunagan WC, Littenberg B, Ewald GA, et al. Randomized trial of a nurse-administered, telephone-based disease management program for patients with heart failure. J Card Fail 2005;11:358–65.
5. Jerant AF, Azari R, Nesbitt TS. Reducing the cost of frequent hospital admissions for congestive heart failure: a randomized trial of a home telecare intervention. Med Care 2001;39:1234–45.
6. Kashem A, Droogan MT, Santamore WP, Wald JW, Bove AA. Managing heart failure care using an internet-based telemedicine system. J Card Fail 2008;14:121–6.
7. Riegel B, Carlson B, Glaser D, Romero T. Randomized controlled trial of telephone case management in Hispanics of Mexican origin with heart failure. J Card Fail 2006;12:211–9.
8. Riegel B, Carlson B, Kopp Z, LePetri B, Glaser D, Unger A. Effect of a standardized nurse case-management telephone intervention on resource use in patients with chronic heart failure. Arch Intern Med 2002;162:705–12.
9. Schwarz KA, Mion LC, Hudock D, Litman G. Telemonitoring of heart failure patients and their caregivers: a pilot randomized controlled trial. Prog Cardiovasc Nurs 2008;23:18–26.
10. Woodend AK, Sherrard H, Fraser M, Stuewe L, Cheung T, Struthers C. Telehome monitoring in patients with cardiac disease who are at high risk of readmission. Heart Lung 2008;37:36–45.
11. Galbreath AD, Krasuski RA, Smith B, et al. Long-term healthcare and cost outcomes of disease management in a large, randomized, community-based population with heart failure. Circulation 2004;110:3518–26.
12. Goldberg LR, Piette JD, Walsh MN, et al. Randomized trial of a daily electronic home monitoring system in patients with advanced heart failure: the Weight Monitoring in Heart Failure (WHARF) trial. Am Heart J 2003;146:705–12.
13. Laramee AS, Levinsky SK, Sargent J, Ross R, Callas P. Case management in a heterogeneous congestive heart failure population: a randomized controlled trial. Arch Intern Med 2003;163:809–17.
14. Barrth V. A nurse-managed discharge program for congestive heart failure patients: outcomes and costs. Home Health Care Manage Pract 2001;13:436–43.
15. Blue L, Lang E, McMurray JJ, et al. Randomised controlled trial of specialist nurse intervention in heart failure. BMJ 2001;323:715–8.
16. DeBusk RF, Miller NH, Parker KM, et al. Care management for low-risk patients with heart failure: a randomized, controlled trial. Ann Intern Med 2004;141:606–13.
17. GESICA Investigators. Randomised trial of telephone intervention in chronic heart failure: DIAL trial. BMJ 2005;331:425.
18. Kasper EK, Gerstenblith G, Hefter G, et al. A randomized trial of the efficacy of multidisciplinary care in heart failure outpatients at high risk of hospital readmission. J Am Coll Cardiol 2002;39:471–80.
19. Krumholz HM, Amatruda J, Smith GL, et al. Randomized trial of an education and support intervention to prevent readmission of patients with heart failure. J Am Coll Cardiol 2002;39:83–9.
20. McDonald K, Ledwidge M, Cahill J, et al. Heart failure management: multidisciplinary care has intrinsic benefit above the optimization of medical care. J Card Fail 2002;8:142–8.
21. Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073–9.
22. Sisk JE, Hebert PL, Horowitz CR, McLaughlin MA, Wang JJ, Chassin MR. Effects of nurse management on the quality of heart failure care in minority communities: a randomized trial. Ann Intern Med 2006;145:273–83.
23. Gambetta M, Dunn P, Nelson D, Herron B, Arena R. Impact of the implementation of telemanagement on a disease management program in an elderly heart failure cohort. Prog Cardiovasc Nurs 2007;22:196–200.
24. Hudson LR, Hamar GB, Orr P, et al. Remote physiological monitoring: clinical, financial, and behavioral outcomes in a heart failure population. Dis Manage 200512;8:372–81.
25. Kielblock B, Frye C, Kottmair S, Hudler T, Siegmund-Schultze E, Middeke M. Impact of telemetric management on overall treatment costs and mortality rate among patients with chronic heart failure. Dtsch Med Wochenschr 2007;132:417–22.
26. Oeff M, Kotsch P, Gosswald A, Wolf U. Monitoring multiple cardiovascular parameters using telemedicine in patients with chronic heart failure. Herzschrittmacherther Elektrophysiol 2005;16:150–8.
27. Roth A, Kajiloti I, Elkayam I, Sander J, Kehati M, Golovner M. Telecardiology for patients with chronic heart failure: the 'SHL' experience in Israel. Int J Cardiol 2004;97:49–55.
28. Scalvini S, Zanelli E, Paletta L, et al. Chronic heart failure home-based management with a telecardiology system: a comparison between patients followed by general practitioners and by a cardiology department. J Telemed Telecare 2006;12 Suppl 1:46–8.
29. Scalvini S, Zanelli E, Volterrani M, et al. A pilot study of nurse-led, home-based telecardiology for patients with chronic heart failure. J Telemed Telecare 2004;10:113–7.
30. Schofield RS, Kline SE, Schmalfuss CM, et al. Early outcomes of a care coordination-enhanced telehome care program for elderly veterans with chronic heart failure. Telemed J E Health 2005;11:20–7.
31. Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol 2003;41:565–71.
32. Morguet AJ, Kuhnelt P, Kallel A, Jaster M, Schultheiss HP. Impact of telemedical care and monitoring on morbidity in mild to moderate chronic heart failure. Cardiology 2008;111:134–9.
33. Myers S. Impact of home-based monitoring on the care of patients with congestive heart failure. Home Health Care Manage Pract 2006;18:444–51.
34. Scalvini S, Capomolla S, Zanelli E, et al. Effect of home-based telecardiology on chronic heart failure: costs and outcomes. J Telemed Telecare 2005;11 Suppl 1:16–8.
35. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. BMJ 2007;334:942.
36. Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. Eur Heart J 2004;25:1570–95.
37. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44:810–9.
38. Roccaforte R, Demers C, Baldassarre F, Teo KK, Yusuf S. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis. Eur J Heart Fail 2005;7:1133–44.
39. Lazarus A. Remote, wireless, ambulatory monitoring of implantable pacemakers, cardioverter defibrillators, and cardiac resynchronization therapy systems: analysis of a worldwide database. Pacing Clin Electrophysiol 2007;30 Suppl 1:S2–12.
40. Patel VL, Shortliffe EH, Stefanelli M, et al. The coming of age of artificial intelligence in medicine. Artif Intell Med 2009;46:5–17.
41. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? N Engl J Med 2000;342:1907–9.
42. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001;286:821–30.

Key Words: device-based monitoring ▪ heart failure ▪ meta-analysis ▪ remote monitoring ▪ outcome.

APPENDIX

For a table showing the study excluded and reason for exclusion as well as funnel plots on cohort and RCT studies, please see the online version of this article.