European Journal of Heart Failure (2017) **19**, 416–425
doi:10.1002/ejhf.626

Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial

Giuseppe Boriani[1,2]*, Antoine Da Costa[3], Aurelio Quesada[4], Renato Pietro Ricci[5], Stefano Favale[6], Gabriele Boscolo[7], Nicolas Clementy[8], Valentina Amori[9], Lorenza Mangoni di S. Stefano[9], and Haran Burri[10], on behalf of the MORE-CARE Study Investigators

[1]University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [2]University of Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy; [3]University Hospital, St. Etienne, France; [4]University General Hospital, Valencia, Spain; [5]San Filippo Neri Hospital, Rome, Italy; [6]University Hospital, Bari, Italy; [7]Chioggia ULSS 14, Chioggia, Italy; [8]Tours University Hospital, Tours, France; [9]Medtronic EMEA Regional Clinical Center, Rome, Italy; and [10]University Hospital of Geneva, Geneva, Switzerland

Received 5 July 2016; revised 27 July 2016; accepted 27 July 2016; online publish-ahead-of-print 26 2016

Aims The aim of this study was to evaluate the clinical efficacy and safety of remote monitoring in patients with heart failure implanted with a biventricular defibrillator (CRT-D) with advanced diagnostics.

Methods and results The MORE-CARE trial is an international, prospective, multicentre, randomized controlled trial. Within 8 weeks of *de novo* implant of a CRT-D, patients were randomized to undergo remote checks alternating with in-office follow-ups (Remote arm) or in-office follow-ups alone (Standard arm). The primary endpoint was a composite of death and cardiovascular (CV) and device-related hospitalization. Use of healthcare resources was also evaluated. A total of 865 eligible patients (mean age 66 ± 10 years) were included in the final analysis (437 in the Remote arm and 428 in the Standard arm) and followed for a median of 24 (interquartile range = 15–26) months. No significant difference was found in the primary endpoint between the Remote and Standard arms [hazard ratio 1.02, 95% confidence interval (CI) 0.80–1.30, $P = 0.89$] or in the individual components of the primary endpoint ($P > 0.05$). For the composite endpoint of healthcare resource utilization (i.e. 2-year rates of CV hospitalizations, CV emergency department admissions, and CV in-office follow-ups), a significant 38% reduction was found in the Remote vs. Standard arm (incidence rate ratio 0.62, 95% CI 0.58–0.66, $P < 0.001$) mainly driven by a reduction of in-office visits.

Conclusions In heart failure patients implanted with a CRT-D, remote monitoring did not reduce mortality or risk of CV or device-related hospitalization. Use of healthcare resources was significantly reduced as a result of a marked reduction of in-office visits without compromising patient safety.
Trial registration: NCT00885677

Keywords Remote monitoring • Cardiac resynchronization therapy • Heart failure • Healthcare • Costs • Outcome

*Corresponding author. Cardiology Department, University of Modena and Reggio Emilia, Policlinico di Modena, Viale del Pozzo, 71, 41124 Modena, Italy. Tel: +39 059 4225836, Fax: +39 059 4224498, Email: giuseppe.boriani@unimore.it

Introduction

Heart failure (HF) is a frequent disease in developed countries and is associated with increased mortality and morbidity, quality of life impairment, and heavy healthcare and economic burden. Data from the ESC-HF Pilot survey[1] conducted in 12 European countries showed post-discharge mortality and readmission rates at 1 year of 17.4% and 31.9%, respectively. More recent data confirmed the important clinical and economic burden of HF hospitalizations.[2,3]

Cardiac resynchronization therapy (CRT) has been shown to reduce mortality and rehospitalization in selected HF patients.[4,5] A recent study from a real-world cohort showed that the risk of hospitalization remains high in recipients of implantable cardioverter defibrillators (ICDs) or biventricular defibrillators for cardiac resynchronization therapy (CRT-D)[6].

Remote monitoring (RM) of implantable cardiac devices can facilitate patient access to healthcare and prompt preventive actions to improve HF outcomes. Several studies demonstrated the safety of RM and its potential impact on patient management, such as the reduction of time to clinical decision,[7–11] number of outpatient visits,[12] and inappropriate shocks.[13] Whether these benefits translate into improved clinical outcomes is still not clear.

The randomized MORE-CARE (MOnitoring Resynchronization dEvices and CARdiac patiEnts) trial was planned to evaluate whether RM may be of higher clinical and/or economic value compared with standard follow-up strategies in the management of systolic HF patients implanted with a CRT-D.

Methods

Study design and patient population

The MORE-CARE is an international, prospective, multicentre, randomized controlled trial involving 61 cardiology centres in nine countries overall, from Europe and Israel. The trial was designed in two phases to demonstrate that RM reduces the time from the onset of a clinically relevant event to clinical decision (Phase 1), and the incidence of all-cause deaths and major cardiovascular (CV) and device-related hospitalizations (Phase 2) compared with standard in-hospital care. Details of the study design and Phase 1 results have already been described.[10,11] In brief, Phase 1 demonstrated that the median delay from device-detected events to clinical decisions was reduced in the remote group compared with the control group [2 (25th–75th percentile, 1–4) days vs. 29 (25th–75th percentile, 3–51) days, $P = 0.004$]. All patients had received *de novo* implant of a Medtronic CRT-D with wireless transmission capabilities within the last 8 weeks before enrolment. Randomization was stratified by centres and performed at enrolment using a centralized electronic system. Patients were randomized 1:1 to undergo remote checks alternating with in-office follow-ups (Remote arm) or in-office follow-ups alone (Standard arm).

The trial was registered at www.clinicaltrials.gov under number NCT00885677.

The study was approved by the Ethics Committee of all participating centres and was conducted in compliance with the Declaration of Helsinki. All patients signed a written informed consent.

Device programming and diagnostic features

Patients in the Remote arm received a Carelink monitor for scheduled remote device checks, and automatic alerts for lung fluid accumulation (OptiVol®), atrial tachyarrhythmia (atrial tachycardia/fibrillation), and system integrity were enabled. In-office device checks were requested to re-arm alerts which had been temporarily inactivated due to previous transmissions. For both arms, audible alerts were disabled, except alerts for system integrity, low battery voltage, excessive charge time, and ventricular fibrillation detection/therapy off. Study flow charts were provided to investigators with the aim to suggest and guide patient remote management.[10]

Data collection

Clinical and device data were collected at enrolment and during scheduled remote checks/in-office visits. Patients in the Remote arm alternated remote checks with in-office visits every 4 months, while the Standard arm received in-office visits every 4 months. Additional data were collected in the case of unscheduled visits or automatic alerts, medical interventions, adverse events, and study deviations. Information about patient and caregiver travel (e.g. distance, time, transport) for in-office visits was also collected.

Study objectives

The primary objective of the MORE-CARE Phase 2 was to evaluate the impact of RM on reducing the 2-year incidence of a composite endpoint including mortality, CV and device-related hospitalizations. Owing to their higher impact on patient morbidity and healthcare costs, only hospitalizations longer than 48 h were included in this primary endpoint evaluation. Each reported event was adjudicated by an independent Event Adjudication Committee to evaluate whether it could be counted as a study endpoint. The Committee included three physicians not involved in the trial and blinded to investigational sites, patient identities, and randomization assignment.

The secondary endpoints were: (i) the utilization of healthcare resources for CV reasons, combining any duration of CV hospitalizations and CV emergency department (ED) admissions together with both scheduled and unscheduled outpatient visits; (ii) the number of hospitalizations, ED admissions, and outpatient visits separately; (iii) the costs related to utilization of healthcare resources for CV and device reasons both from the healthcare and from the patient perspective; and (iv) the safety of RM in CRT-D patient management.

The methods adopted for monetary valuations of healthcare costs are reported in the Supplementary material online (*Table S1*).

Sample size

The study sample size calculations have already been decribed.[10] In brief, sample size was calculated to compare the 2-year incidence of the composite endpoint, assuming an event rate of 30% in the Standard arm and a target of 20% relative hazard reduction in the Remote arm, with a power of 90% and a confidence interval (CI) of 95%. Up to seven interim analyses and the final analysis were planned at pre-specified time points to reach a maximum sample of 1720 patients. With an expected enrolment rate of 336 patients per year, the estimated study duration was ~4 years. The protocol included the option to prolong

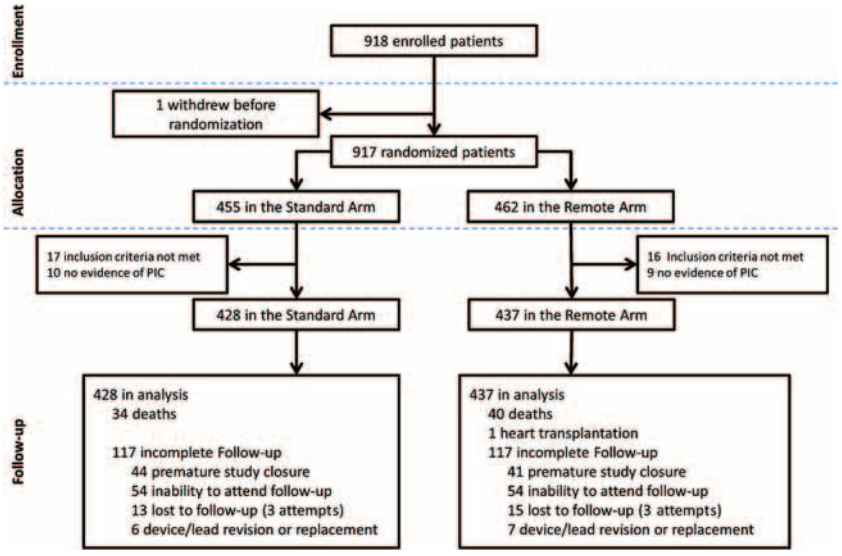

Figure 1 Study flow chart. PIC, patient informed consent form.

or shorten the study duration in the case of a slower or faster rate of enrolment, respectively.

Statistical analysis

The analysis set was made up of all randomized patients and included data of the 2-year follow-up period. Crossovers between randomization arms were not admitted in the study design; consequently, data were analysed according to the per-protocol principle. Further details on statistical analysis are given in the Supplementary material online (*Table S1*).

All tests were adjusted for centre and any unbalanced baseline characteristic. An alpha-level of 0.05 was considered for each test. All statistical analyses were performed using SAS 9.3 version software (SAS Institute Inc., Cary, NC, USA).

Early study closure

In July 2014, the Steering Committee decided to terminate the study prematurely because of a lower than expected enrolment rate (36 patients in the last months) leading to an unrealistic prolongation of the enrolment period. As a consequence, no additional patients were enrolled and ongoing patients were followed until 30 April 2015 to ensure a minimum follow-up of 8 months for the last patients.

Results

Recruitment and population description

From May 2009 to July 2014, a total of 918 patients were enrolled in the study. One patient withdrew before randomization, 462 patients were randomly assigned to the Remote arm, and 455 to the Standard arm (*Figure 1*). Twenty-five and 27 patients from the Remote and Standard arm, respectively, were excluded from the analysis set for either unmet inclusion/exclusion criteria or missing evidence of an informed consent form in the centre at the time of the monitoring visit.

Characteristics of the 865 included patients were balanced between the study arms (*Table 1*) except for gender, history of AF, and atrioventricular block. Mean age at enrolment was 66 ± 10 years, and 76% of patients were men. Forty-four per cent of patients had ischaemic heart disease, 27% had a history of AF, and 12% had a history of sustained ventricular arrhythmias. Mean LVEF was 27 ± 6%. Thirty-eight per cent of patients were in NYHA class II at the time of enrolment, with clinical improvement as compared with NYHA class before CRT-D device implantation (all the patients were in NYHA class III–IV before implant).

The median follow-up was 24 months for both arms, with an interquartile range (IQR) of 15–25 months and 14–26 months in the Remote and Standard arm, respectively. Total exposure time was 707 patient-years in the Remote arm and 696 patient-years in the Standard arm. All randomized patients who met the inclusion/exclusion criteria were included in the analysis until study exit or death. Follow-up compliance was 94% in both arms: 1806 (867 in-office visits) out of 1913 (877 in-office visits) in the Remote arm vs. 1789 out of 1912 in the Standard arm ($P = 0.54$).

Primary composite endpoint (deaths, cardiovascular or device-related hospitalizations)

Overall, 253 patients reached the primary composite endpoint, 130 (29.7%) in the Remote arm and 123 (28.7%) in the Standard arm: the Kaplan–Meier 2-year risk estimates were 34.3% (95% CI 29.7–39.4) and 32.7% (95% CI 28.2–37.8), respectively ($P = 0.89$, *Figure 2*).

Table 1 Patient characteristics at enrolment (0–8 weeks after biventricular defibrillator implantation)

Baseline characteristics	Remote arm ($n = 437$)	Standard arm ($n = 428$)
Demographic characteristics		
Age (years), mean ± SD	66 ± 11	67 ± 10
Male, *n* (%)	342 (78.8)	312 (73.1)*
Medical and surgical history		
Ischaemic cardiomyopathy, *n* (%)	185 (42.8)	193 (45.3)
Myocardial infarction, *n* (%)	164 (38.5)	173 (40.7)
History of atrial arrhythmias, *n* (%)	126 (29.2)	104 (24.5)
History of AF, *n* (%)	89 (20.7)	62 (14.7)**
History of sustained VT/VF, *n* (%)	53 (12.4)	46 (10.8)
Complete AV block, *n* (%)	18 (4.3)	31 (7.4)*
AV node ablation, *n* (%)	2 (0.5)	2 (0.5)
Left bundle branch block, *n* (%)	310 (73.1)	317 (76.0)
QRS (ms), mean ± SD	152 ± 29	155 ± 29
Valvular alteration, *n* (%)	208 (48.5)	194 (46.0)
Previous valvular surgery, *n* (%)	41 (9.6)	36 (8.5)
History of syncope, *n* (%)	48 (11.3)	52 (12.3)
Diabetes, *n* (%)	132 (31.3)	154 (37.0)
Hypertension, *n* (%)	198 (46.2)	171 (40.8)
Previous TIA or stroke, *n* (%)	37 (8.7)	26 (6.2)
COPD, *n* (%)	61 (14.2)	66 (15.6)
NYHA class III or IV at enrolment, *n* (%)	265 (62.9)	258 (61.1)
Worsening of HF during the year before implant, *n* (%)	30 (7.2)	22 (5.3)
LVEF (%), mean ± SD	27.3 ± 6.6	27.4 ± 6.0
Medications at enrolment		
Diuretic, *n* (%)	386 (91.7)	382 (91.2)
Beta-blocker, *n* (%)	375 (89.1)	370 (88.3)
ACE inhibitor or ARB, *n* (%)	347 (82.4)	331 (79.0)
Aldosterone antagonists	132 (31.5)	128 (30.4)
Antiarrhythmic, *n* (%)	116 (27.6)	101 (24.1)
Antiplatelet, *n* (%)	263 (62.5)	250 (59.7)
OAC, *n* (%)	104 (24.7)	84 (20.0)
Nitrates, *n* (%)	52 (12.4)	48 (11.5)

*P-value = 0.049; **P-value = 0.020.
HF, heart failure; OAC, oral anticoagulants; TIA, transient ischaemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

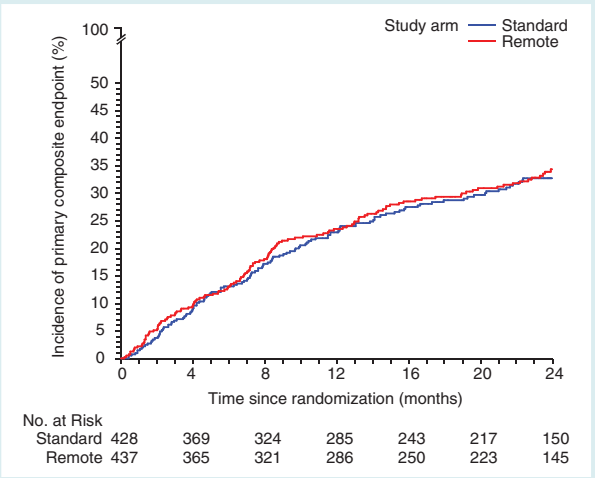

Figure 2 Kaplan–Meier estimates of the primary composite endpoint.

No significant differences were found in the individual components of the primary endpoint (all $P > 0.05$, *Table 2*). The most frequent component of the primary endpoint was CV hospitalizations, whose Kaplan–Meier 2-year estimates were 27.3% (95% CI 22.9–32.2) in the Remote arm and 26.7% (95% CI 22.4–31.6) in the Standard arm ($P = 0.80$).

During the course of the study, 74 patients died: 40 (9.2%) in the Remote arm and 34 (7.9%) in the Standard arm. The Kaplan–Meier 2-year mortality estimates were 11.2% (95% CI 8.3–15.1) and 9.4% (95% CI 6.8–12.9), respectively ($P = 0.59$). The 2-year CV mortality rates were 8.2% (95% CI 5.7–11.7) and 7.8% (95% CI 5.4–11.1), respectively ($P = 0.87$, Kaplan–Meier curve reported in the Supplementary material online, *Figure S1*).

Use of healthcare resources for cardiovascular reasons

The burden of healthcare resource utilization for CV reasons was 38% lower in the Remote vs. the Standard arm [incidence rate ratio (IRR) 0.62, 95% CI 0.58–0.66, $P < 0.001$, *Figure 3*], with 2-year rates of 3.7 (95% CI 3.5–3.9) and 6.0 (95% CI 5.7–6.2) per 100 patients, respectively. As shown in *Table 3*, 649 hospitalizations were reported, 337 in the Remote arm and 312 in the Standard arm. The all-cause hospitalization rates, estimated as the 2-year rate per 100 patients, were 96 (95% CI 86–106) and 90 (95% CI 80–100, p = 0.83), respectively. Hospitalizations for CV reasons were 197 (111 due to HF) and 200 (103 due to HF) in the Remote and Standard arm, respectively. During the study, there were 106 ED admissions (*Table 3*) not followed by a hospitalization, with a significantly lower occurrence in the Remote arm (IRR 0.72, 95% CI 0.53–0.98, $P = 0.04$). As shown in *Table 3*, RM led to a significant reduction in total visits (IRR 0.59, 95% CI 0.56–0.62, $P < 0.001$), with more frequent unscheduled visits compared with the Standard arm (IRR 2.80, 95% CI 2.16–3.63, $P < 0.001$).

Table 2 Results of the primary outcome and its components

	Remote arm ($n = 437$)	Standard arm ($n = 428$)	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint, *n* (%)				
Death or first CV or device-related hospitalization (≥48 h stay)	130 (29.7)	123 (28.7)	1.02 (0.80–1.30)	0.889
Components, *n* (%)				
Death from any cause	40 (9.2)	34 (7.9)	1.13 (0.71–1.80)	0.594
First CV hospitalization	100 (22.9)	97 (22.7)	0.96 (0.73–1.28)	0.796
First device-related hospitalization	17 (3.9)	18 (4.2)	0.89 (0.44–1.79)	0.742

CI, confidence interval; CV, cardiovascular.

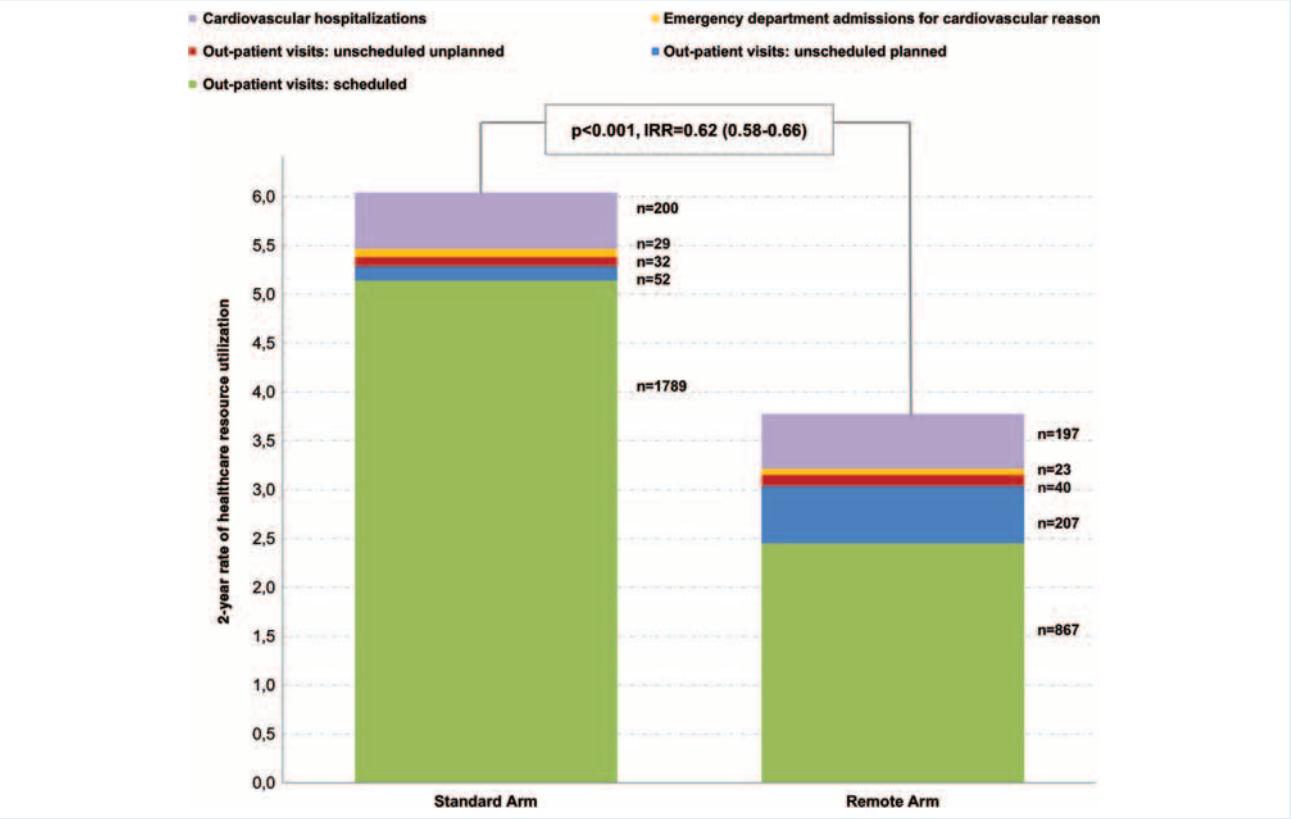

Figure 3 Two-year rates per randomization group of scheduled outpatient visits, unscheduled planned and unplanned outpatient visits, and cardiovascular emergency department admissions and hospitalizations. For each randomization group and type of visit, the total number of occurrences is displayed beside the corresponding bar. IRR incidence rate ratio.

Costs for cardiovascular and device-related events from the National Healthcare System perspective

Costs related to healthcare resource utilization for CV and device-related reasons are shown in *Table 4*. When considering the estimated costs for the review of device transmissions in the Remote arm, the cost saving from RM was €2899 per 100 patients at 2 years (*Table 4*).

Costs for visits and device checks from the perspective of the patient budget

Information about patient and caregiver travel to and from the hospital showed an average distance between patient's home and hospital of 52 km, and the average time required for a one-way journey was 50 min. In 66% of visits, patients were accompanied by a relative, and in 5% by an acquaintance or nurse or caregiver. The majority of journeys (77%) were made by car; other modes of transportation included local transport by bus (11%), taxi (6%), and train (3%). The estimated 2-year expenses for patient travelling

Table 3 Hospitalizations, emergency department admissions, and outpatient visits: event rates related to use of healthcare resources.

HCU type	Events (no. of patients with HCU)		2-year rate of hospitalizations per 100 patients (95% CI)		Adjusted IRR (95% CI)	*P*-value
	Remote arm ($n = 437$)	Standard arm ($n = 428$)	Remote arm ($n = 437$) (707 FU years)	Standard arm ($n = 428$) (696 FU years)		
Hospitalizations						
Hospitalizations for any reason	337 (165)	312 (151)	96 (86–106)	90 (80–100)	1.02 (0.83–1.26)	0.833
Cardiovascular hospitalizations	197 (111)	200 (112)	56 (48–64)	58 (50–66)	0.91 (0.72–1.15)	0.418
HF hospitalizations	111 (63)	103 (60)	32 (26–38)	30 (24–36)	0.97 (0.74–1.29)	0.846
Device-related hospitalizations	24 (20)	22 (21)	6.8 (4.6–10.2)	6.2 (4.2–9.6)	1.16 (0.82–1.65)	0.399
ED admissions not leading to hospitalization						
ED admissions for any reason	40 (27)	56 (41)	11.4 (8.4–15.4)	16.0 (12.4–20.0)	0.72 (0.53–0.98)	0.037
Cardiovascular ED admissions	23 (15)	29 (24)	6.6 (4.4–9.8)	8.4 (5.8–12.0)	0.78 (0.55–1.09)	0.142
HF-related ED admission	14 (8)	17 (14)	4.0 (2.4–6.6)	4.8 (3.0–7.8)	0.78 (0.54–1.12)	0.180
Device-related ED admissions	7 (7)	2 (2)	2.0 (1.0–4.2)	0.6 (0.2–2.2)	3.53 (2.19–5.68)	<0.001
Outpatient visits						
All visits	1114 (315)	1873 (538)	316 (297–334)	538 (515–563)	0.59 (0.56–0.62)	<0.001
Scheduled visits	867 (367)	1789 (393)	246 (230–262)	514 (490–538)	0.48 (0.46–0.50)	<0.001
Unscheduled visits	247 (140)	84 (61)	70 (62–80)	24 (19–30)	2.80 (2.16–3.63)	<0.001

CI, confidence interval; ED, emergency department; FU, follow-up; HCU, healthcare resource utilization; IRR, incidence rate ratio.

Table 4 Costs related to the use of healthcare resources for cardiovascular and device-related events and cost savings in the perspective of the Italian Healthcare System

HCU type	Unit cost (€)	2-year cost × 100 patients (95% CI)		2-year cost saving × 100 patients (€)
		Remote arm	Standard arm	
Cardiovascular and device-related hospitalizations				
Cardiovascular hospitalizations	€4432	€248 192 (213 000–284 000)	€257 056 (222 000–293 000)	€8864
Device-related hospitalizations	€4432	€30 137 (20 000–45 000)	€27 478 (19 000–43 000)	–€2659
Cardiovascular and device-related ED admissions not leading to hospitalization				
Cardiovascular ED admissions	€241	€1591 (1060–2362)	€2024 (1398–2892)	€433
Device-related ED admissions	€241	€482 (241–1012)	€145 (48–530)	–€337
Outpatient visits, in-office for cardiovascular or device-related reasons				
Scheduled visit	€27.90	€6863 (6400–7300)	€14 341 (13 700–15 000)	€7478
Unscheduled visit	€27.90	€1953 (1700–2200)	€670 (500–800)	–€1283
Remote device checks				
Scheduled remote device check	€0–13.95	€0–€3710	€0	€0–€3710
Unscheduled remote device check	€0–13.95	€0–€5887	€0	€0–€5887
Total				
Scenario 1	No reimbursement for remote device check	€28 918	€301 714	€12 496
Scenario 2	Remote device check reimbursed as 1/2 in-office	€298 815	€301 714	€2899

CI, confidence interval; ED, emergency department; HCU, healthcare resource utilization.

to the hospital were €373 in the Remote arm and €518 in the Standard arm (i.e. a cost saving of €145 resulting from RM).

Automatic alert transmissions

In the Remote arm, 5670 alerts were identified and 4683 (82.6%) were successfully transmitted. Among the 987 failed transmissions, 361 transmissions failed because the patients were already in the hospital. By excluding these transmissions, the successful transmission rate rose to 88.2%. Other reasons for transmission failure were: monitor set off, phone line connection problems, or patient's temporary absence from home.

Quality of life

The patient's quality of life was investigated by means of the Minnesota Living With Heart Failure Questionnaire. Baseline values were comparable between the Remote (26, IQR 12–49) and Standard (27, IQR 11–46, $P = 0.46$) arms. The changes in quality of life from baseline to 16-month follow-up were similar in the Remote arm (15, IQR 6–30) and Standard arm (10, IQR 3–26, $P = 0.29$). As reported in detail in the Supplementary material online (*Figure S1*), in both groups quality of life significantly improved at follow-up vs. baseline ($P < 0.001$).

Safety issues

Adverse events analysis showed that clinical use of RM did not raise any safety issue: there were 55 adverse events related to the implanted system in the Remote arm and 53 in the Standard arm with 2-year rates of 15.6 (95% CI 11.9–20.3) and 15.2 (95% CI 11.6–19.9) per 100 patients, respectively ($P = 0.92$).

Discussion

Remote monitoring is proposed as a tool for changing the management of HF patients with an implanted device,[14] aiming to improve patient outcome, as well as to reduce the use of resources and costs for both healthcare systems and patients. The present study was focused on a specific population of patients with pre-implant NYHA class III–IV, expected to face a greater number of events and having complex and time-consuming follow-up needs.

Remote monitoring, mortality and cardiovascular hospitalizations

The present randomized controlled trial showed that, in patients with systolic HF and implanted with a CRT-D with automated alerts for pulmonary congestion and atrial arrhythmias, RM is not associated with a benefit on mortality or risk of CV or device-related hospitalization. These findings are in line with the results of a recent meta-analysis of 11 randomized controlled trials[15] that showed no significant effect of RM either on all-cause mortality or on cardiac mortality in HF patients implanted with cardiac implantable electrical devices. More recently, the OptiLink HF study[16] tested a specific intrathoracic impedance and telemedicine-based HF disease management strategy, showing no effect of telemonitoring on all-cause death or CV hospitalizations in patients with moderate to severe HF and implanted with an ICD/CRT-D. The IN-TIME trial is the only study that showed a positive effect of RM on patient survival, with a reduced mortality in the remote arm, but without effects on hospitalizations for worsening of HF[17]. It is noteworthy that 1-year mortality in the Standard arm of IN-TIME was 1.8-fold that observed in the Standard arm of MORE-CARE (8.7% vs. 4.8%), thus indicating differences in patient population characteristics that may have affected the finding of a beneficial effect on hard outcomes.

Hospitalizations for HF accounted for only around one-third of all admissions in our study. Real-world data have shown that co-morbidities significantly and independently affect both all-cause and HF hospitalizations,[6,18] and may therefore mitigate the impact of RM. It seems clear that, according to evidence from systematic reviews,[15] recent studies,[16] and the present trial, RM of HF patients, when applied for the purpose of disease management, does not significantly decrease hospital admissions. Nevertheless, our data show that RM with advanced diagnostics for HF is safe and does not compromise outcome. This is in contrast to the use of audible alerts for transthoracic impedance monitoring, which has been shown to increase HF hospitalizations and outpatient visits in the DOT-HF trial.[19]

Remote monitoring transmission reliability

An important aspect for widespread implementation of RM is reliability of transmissions. In our study, 88.2% of alerts were properly transmitted, which is an improvement compared with previous reports.[8,16] This may be due to better patient education together with technical improvements and more experience with RM compared with earlier studies.

Healthcare resource utilization

In the present study, we decided to analyse clinical and economic benefits together, since both are relevant for the healthcare system.[20] The positive results found in the present study are related to a 41% reduction in scheduled outpatient visits, despite a small increase in unscheduled visits, but no increase in ED admissions. This net benefit has interesting implications for re-organization of care, with financial benefits for both the healthcare system and the patients. The reduction in scheduled outpatients visits appears important because most of device follow-ups are routine checks with no actionable events or device programming.[21]

Economic analyses focusing on RM of cardiac devices are growing, but comparisons across studies are challenged by differences in study design and issues specific to this type of analysis, such as costing methodologies and the perspective adopted (societal, payer, or provider).

In the present study, RM had a favourable profile in terms of costs, from the perspective of both the healthcare system and that of the patient. This may be a valid reason for implementing RM despite the lack of impact on hard clinical outcomes. Moreover,

RM may be more efficient than traditional in-office follow-up, with allocation of resources to other tasks.[21]

A number of reports have evaluated resource use and costs related to RM.[22–29] Reductions in staff time and associated costs have been consistently reported in several studies,[23,29] with the exception of the EuroEco study,[22] where costs were comparable for device checks based on remote vs. conventional in-office visits.

Results related to costs for healthcare resource utilization are variable: Fauchier,[25] Raatikainen,[23] Zanaboni,[24] and Guédon-Moreau[26] reported or assumed savings (due to reduced visits or hospitalizations, and/or reimbursed transports), whereas Al-Khatib,[27] Burri,[28] and Heidbuchel[22] did not. This reflects the variable results of RM studies in terms of outcomes, including number of visits and hospitalizations. In a recent meta-analysis, Klersy *et al.*[15] reported that standard follow-up is associated with higher costs, in the range of 10–55%, as compared with RM, and that the benefit is likely to be due to a reduction in planned visits. Our findings are an additional contribution to the field with regard to savings that can be achieved from the perspective of the healthcare system. Furthermore, MORE-CARE has also shown a benefit in terms of patient costs related to transportation. Another randomized study (REM-HF[30]) is going to assess RM in HF when applied to a large number of individuals at nine UK hospitals, taking into account clinical endpoints (all-cause death or unplanned hospitalization as the primary endpoint), as well as economic endpoints. The latter include the cost per quality-adjusted life years, with direct costs estimated from the National Health Service perspective. Both patients with CRT devices and patients with ICDs are included.[30]

Finally, costs for performing RM were often not taken into account in previous economic analyses on RM. This may be linked to the absence of reimbursement in most countries. In MORE-CARE, savings in the RM arm were maintained despite taking into account payment for remote device management.

Limitations

Although the present study was underpowered to evaluate the primary endpoint because of premature termination, it provides some data to be evaluated according to the literature, which in general is in line with our findings, if the primary endpoint and its components are considered.[15]

The present analyses excluded some randomized subjects because those implanted with a CRT-D, or unable to use the CareLink System, were not considered in the analysis set. Despite having provided flow charts for managing specific alerts, clinical practice was likely to have varied between different study centres. This reflects daily practice and the complexity of HF management. Furthermore, automatic alerts for HF monitoring were programmed only for AF and thoracic impedance, with no activation for several parameters—heart rate variability, nocturnal heart rate, and patient activity—that have recently been the subject of investigation for improving prediction of HF worsening.[31]

The economic benefit was based on some assumptions and on tariffs derived from the Italian context, where most of the patients were recruited (52.7%). Since the tariffs for in-office visits may be higher in other countries,[32] the extent of monetary savings that could be achieved may be underestimated by the current analysis. Finally, in our economic analysis we did not consider the perspective of the provider, but focused on that of the healthcare system and the patient.

Conclusions

In HF patients implanted with a CRT-D, RM did not reduce mortality or risk of CV or device-related hospitalization. Despite the lack of benefit on clinical outcomes, the use of RM had a positive impact on the use of healthcare resources, with a 41% reduction of in-office visits, without compromising patient safety. The favourable profile in terms of cost savings of RM vs. standard follow-up emerged from the perspective of the healthcare system as well as from that of the patient.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sources for unit cost estimates.

Figure S1. Kaplan–Meier survival curve for total mortality.

Appendix S1. Full list of MORE-CARE Investigators.

Acknowledgements

We thank Francesco de Seta, PhD, Xavier Navarro, MD, Andrea Grammatico, PhD, and Arnaldo Risi, PhD for scientific support for the study.

Funding

The MORE-CARE trial was sponsored by Medtronic organizations of the participating countries.

Conflict of interest: L.M. and V.A. are Medtronic plc employees. G.B. reported speaker's fees from Medtronic, Boston Scientific, and Boehringer Ingelheim. N.C. reported consulting fees from Medtronic, Boston Scientific, St Jude Medical, and Sorin-Livanova. A.Q. reported consulting fees from Medtronic and St Jude Medical. R.R. reported consulting fees from Medtronic and the Sorin Group. H.B. reported speaker fees and institutional fellowship support from Medtronic. The remaining authors reported no conflicts of interest.

References

1. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L. EURObservational research programme: the Heart Failure Pilot survey (ESC-HF Pilot). *Eur J Heart Fail* 2010;**12**:1076–1084.
2. Khan H, Greene SJ, Fonarow GC, Kalogeropoulos AP, Ambrosy AP, Maggioni AP, Zannad F, Konstam MA, Swedberg K, Yancy CW, Gheorghiade M, Butler J; EVEREST Trial Investigators. Length of hospital stay and 30-day readmission following heart failure hospitalization: insights from the EVEREST trial. *Eur J Heart Fail* 2015;**17**:1022–1031.
3. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Bohm M, Lewis EF, Zannad F, Gheorghiade M; ASTRONAUT Investigators and Coordinators. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: Findings from the ASTRONAUT trial. *Eur J Heart Fail* 2015;**17**:591–600.

4. Bristow MR, Saxon L a, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
5. Cleland J, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
6. Boriani G, Berti E, Maria L, Belotti B, Biffi M, Palma R De, Malavasi VL, Bottoni N, Rossi L, De Maria E, Mantovan R, Zardini M, Casali E, Marconi M, Bandini A, Tomasi C, Boggian G, Barbato G, Toselli T, Zennaro M, Sassone B, Romagna E; RERAI (Registry of Emilia Romagna on Arrhythmia Interventions) Investigators. Cardiac device therapy in patients with left ventricular dysfunction and heart failure: 'real-world' data on long-term outcomes (mortality, hospitalizations, days alive and out of hospital). *Eur J Heart Fail* 2016; **18:**693–702.
7. Varma N, Epstein AE, Irimpen A, Schweikert R, Love C; TRUST Investigators. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Safely Reduces Routine Office Device Follow-Up (TRUST) Trial. *Circulation* 2010;**122**:325–332.
8. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH; CONNECT Investigators. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol* 2011;**57**:1181–1189.
9. Landolina M, Perego GB, Lunati M, Curnis A, Guenzati G, Vicentini A, Parati G, Borghi G, Zanaboni P, Valsecchi S, Marzegalli M. Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study. *Circulation* 2012;**125**:2985–2992.
10. Burri H, Quesada A, Ricci RP, Boriani G, Davinelli M, Favale S, Da Costa A, Kautzner J, Moser R, Navarro X, Santini M. The MOnitoring Resynchronization dEvices and CARdiac patiEnts (MORE-CARE) study: rationale and design. *Am Heart J* 2010;**160**:42–48.
11. Boriani G, Da Costa A, Ricci RP, Quesada A, Favale S, Iacopino S, Romeo F, Risi A, Mangoni di S Stefano L, Navarro X, Biffi M, Santini M, Burri H; MORE-CARE Investigators. The MOnitoring Resynchronization dEvices and CARdiac patiEnts (MORE-CARE) randomized controlled trial: phase 1 results on dynamics of early intervention with remote monitoring. *J Med Internet Res* 2013;**15**:e167.
12. Hindricks G, Elsner C, Piorkowski C, Taborsky M, Geller JC, Schumacher B, Bytesnik J, Kottkamp H. Quarterly vs. yearly clinical follow-up of remotely monitored recipients of prophylactic implantable cardioverter-defibrillators: results of the REFORM trial. *Eur Heart J* 2014;**35**:98–105.
13. Guédon-Moreau L, Lacroix D, Sadoul N, Clémenty J, Kouakam C, Hermida JS, Aliot E, Boursier M, Bizeau O, Kacet S; ECOST Trial Investigators. A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial. *Eur Heart J* 2013;**34**:605–614.
14. Boriani G, Diemberger I, Martignani C, Biffi M, Valzania C, Bertini M, Domenichini G, Saporito D, Ziacchi M, Branzi A. Telecardiology and remote monitoring of implanted electrical devices: the potential for fresh clinical care perspectives. *J Gen Intern Med* 2008;**23**:73–77.
15. Klersy C, Boriani G, Silvestri A De, Mairesse GH, Braunschweig F, Scotti V, Balduini A, Cowie MR, Leyva F; Health Economics Committee of the European Heart Rhythm Association. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized, controlled trials in patients with heart failure. *Eur J Heart Fail* 2016;**18**:195–204.
16. Böhm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, Klein G, Gerritse B, Monteiro J, Israel C, Bimmel D, Käab S, Huegl B, Brachmann J; OptiLink HF Study Investigators. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J* 2016 Mar 16. pii: ehw099 [Epub ahead of print].
17. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Søgaard P; IN-TIME Study Group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
18. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2013; **16**:103–111.
19. Van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M; DOT-HF Investigators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation* 2011;**124**:1719–1726.
20. Boriani G, Maniadakis N, Auricchio A, Müller-Riemenschneider F, Fattore G, Leyva F, Mantovani L, Siebert M, Willich SN, Vardas P, Kirchhof P. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J* 2013;**34**:1869–1874.
21. Boriani G, Auricchio A, Klersy C, Kirchhof P, Brugada J, Morgan J, Vardas P. Healthcare personnel resource burden related to in-clinic follow-up of cardiovascular implantable electronic devices: a European Heart Rhythm Association and Eucomed joint survey. *Europace* 2011;**13**:1166–1173.
22. Heidbuchel H, Hindricks G, Broadhurst P, Van Erven L, Fernandez-Lozano I, Rivero-Ayerza M, Malinowski K, Marek A, Garrido RFR, Loscher S, Beeton I, Garcia E, Cross S, Vijgen J, Koivisto U-M, Peinado R, Smala A, Annemans L. EuroEco (European Health Economic Trial on Home Monitoring in ICD Patients): a provider perspective in five European countries on costs and net financial impact of follow-up with or without remote monitoring. *Eur Heart J* 2015;**36**: 158–169.
23. Raatikainen MJ, Uusimaa P, Van Ginneken MM, Janssen JP, Linnaluoto M. Remote monitoring of implantable cardioverter defibrillator patients: a safe, time-saving, and cost-effective means for follow-up. *Europace* 2008;**10**:1145–1151.
24. Zanaboni P, Landolina M, Marzegalli M, Lunati M, Perego GB, Guenzati G, Curnis A, Valsecchi S, Borghetti F, Borghi G, Masella C. Cost–utility analysis of the EVOLVO study on remote monitoring for heart failure patients with implantable defibrillators: randomized controlled trial. *J Med Internet Res* 2013;**15**:e106.
25. Fauchier L, Sadoul N, Kouakam C, Briand F, Chauvin M, Babuty D, Clementy J. Potential cost savings by telemedicine-assisted long-term care of implantable cardioverter defibrillator recipients. *Pacing Clin Electrophysiol* 2005;**28** Suppl 1:S255–S259.
26. Guédon-Moreau L, Lacroix D, Sadoul N, Clémenty J, Kouakam C, Hermida JS, Aliot E, Kacet S; ECOST Trial Investigators. Costs of remote monitoring vs. ambulatory follow-ups of implanted cardioverter defibrillators in the randomized ECOST study. *Europace* 2014;**16**:1181–1188.
27. Al-Khatib SM, Piccini JP, Knight D, Stewart M, Clapp-Channing N, Sanders GD. Remote monitoring of implantable cardioverter defibrillators versus quarterly device interrogations in clinic: results from a randomized pilot clinical trial. *J Cardiovasc Electrophysiol* 2010;**21**:545–550.
28. Burri H, Sticherling C, Wright D, Makino K, Smala A, Tilden D. Cost–consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK. *Europace* 2013;**15**:1601–1608.
29. Elsner CH, Sommer P, Piorkowski C, Taborsky M, Neuser H, Bytesnik J, Geller JC, Kottkamp H, Wiesmeth H, Hindricks G. A prospective multicenter comparison trial of Home Monitoring against regular follow-up in MADIT II patients: additional visits and cost impact. *Comput Cardiol* 2006; **33**:241–244.
30. Morgan JM, Dimitrov BD, Gill J, Kitt S, Andre Ng G, McComb JM, Raftery J, Roderick P, Seed A, Williams SG, Witte KK, Jay Wright D, Yao GL, Cowie MR. Rationale and study design of the REM-HF study: remote management of heart failure using implanted devices and formalized follow-up procedures. *Eur J Heart Fail* 2014;**16**:1039–1045.
31. Whellan DJ, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, Pavri BB, O'Connor CM; PARTNERS Study Investigators. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations. Results From PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. *J Am Coll Cardiol* 2010;**55**:1803–1810.
32. Boriani G. Remote monitoring of cardiac implantable electrical devices in Europe: Quo vadis? *Europace* 2015;**17**:674–676.