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REVIEW

Remote monitoring of implantable cardioverter-defibrillators and resynchronization devices to improve patient outcomes: dead end or way ahead?

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Remote monitoring (RM) has become a new standard of care in the follow-up of patients with implantable pacemakers and defibrillators. While it has been consistently shown that RM enables earlier detection of clinically actionable events compared with traditional in-patient evaluation, this advantage did not translate into improved patient outcomes in clinical trials of RM except one study using daily multiparameter telemonitoring in heart failure (HF) patients. Therefore, this review, focusing on RM studies of implantable cardioverter-defibrillators and cardiac resynchronization therapy defibrillators in patients with HF, discusses possible explanations for the differences in trial outcomes. Patient selection may play an important role as more severe HF and concomitant atrial fibrillation have been associated with improved outcomes by RM. Furthermore, the technical set-up of RM may have an important impact as a higher level of connectivity with more frequent data transmission can be linked to better outcomes. Finally, there is growing evidence as to the need of effective algorithms ensuring a fast and well-structured clinical response to the events detected by RM. These factors re-emphasize the potential of remote management of device patients with HF and call for continued clinical research and technical development in the field.

Keywords Remote monitoring • Heart failure • Outcome studies • Mortality • Atrial fibrillation • Implantable cardioverter-defibrillator • Cardiac resynchronization therapy

Introduction

Remote monitoring (RM) of cardiovascular implantable electronic devices (CIEDs) was initially introduced to supplement compulsory calendar-based in-person evaluations (IPE), to provide convenience to patients and clinics, and to monitor device function.[1,2] Subsequent clinical trials consistently showed comparative advantages of RM-based follow-up over IPE alone, including a reduction of IPE frequency with maintained patient safety and early detection of clinically actionable events.[3–10] Furthermore, RM+IPE was associated with improved patient satisfaction, quality of life, and adherence to follow-up schedule compared with IPE alone.[10–14] In 2015, a transatlantic expert board recommended implant-based RM as a new standard of care in which individualized and alert-driven IPE should replace most routine follow-ups.[15]

The natural extension of RM applications is to improve patient outcomes. However, results so far have been neutral on this count,[6,7,15–22] with the exception of one randomized trial (IN-TIME) showing advantage of daily multiparameter telemonitoring over IPE in heart failure (HF) patients.[23] This observation arouses curiosity. Since patients enrolled among the trials have been similar, potential reasons for the unique result of IN-TIME may include differences in the remote technology utilized (i.e. transmission frequency and prioritization) and/or interventions undertaken in response to received data.

The present review discusses the possible impact of these differences on patient outcomes in recent studies.[15,24] As the vast majority of

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randomized controlled trials (RCTs) have enrolled HF patients with implantable cardioverter-defibrillators (ICDs) or cardiac resynchronization therapy defibrillators (CRT-Ds), we focused on clinical endpoints relevant to these groups: all-cause mortality, cardiovascular (CV) mortality, and CV hospitalization.

Remote monitoring platforms

Different technologies for remote CIED monitoring transmit multiple parameters from device memory, such as lead parameters and battery status, arrhythmias, intracardiac electrograms, details on therapy delivery, heart rate and rhythm statistics, and patient activity levels.[17,23,25–28] Some platforms can monitor intrathoracic impedance as a measure of pulmonary fluid status and potential early sign of cardiac decompensation.[27,29] One platform offers optional transmission of patient weight, blood pressure, and HF symptoms.[26,27,30] All platforms store transmitted data in the manufacturer's central repository and send automated e-mail, SMS, or fax alert notifications to caregivers if pre-specified modifiable criteria are met.[15,23,26,27] Clinicians can view all transmitted data on a secure dedicated website (*Figure 1*).

Despite these many commonalities, the frequency and success of routine and/or alert data transmission—and thus the level of connectivity—used to vary considerably among RM platforms. One platform, used in IN-TIME, sent data in 24-h intervals and transmissions were successful on >85% of patient days ('high temporal resolution RM').[9,23,31–33] Other platforms mainly sent data in one- to three-week intervals (as default although programmable to daily)[15,34,35] and additional alert notifications upon detection of pre-specified out-of-bounds parameters (e.g. arrhythmia episodes, impedance changes, lead issues) or triggered by patients, where this complement of alert-based notifications also differed among manufacturers.[36] The success rate of non-scheduled transmissions was often low (~50%)[6,18,21,37] since several factors could hinder delivery of remote data and alerts.[6,15,35,38] When prospectively tested, fully automated daily messaging systems provided early detection more effectively.[8,39]

Systematic reviews and meta-analyses of randomized trials

In 2015, Parthiban *et al.*[19] performed a meta-analysis of seven RCTs comprising 4932 ICD or CRT-D patients followed for 12–24 months. All-cause mortality did not differ significantly for RM+IPE vs. IPE alone, with an odds ratio of 0.83 [95% confidence interval (CI) 0.58–1.17, $P = 0.28$]. Of seven trials, only IN-TIME reported a significant reduction in the secondary endpoint of all-cause mortality [Kaplan–Meier estimate at 1 year: 3.4% RM vs. 8.7% controls, hazard ratio (HR) 0.36, 95% CI 0.17–0.74; $P = 0.004$] (*Table 1*) and in CV mortality (2.7% RM vs. 6.8% controls, HR 0.37, 95% CI 0.16–0.83; $P = 0.012$) (*Table 2*).[19,23] When outcomes of all trials utilizing daily automatic RM vs. other systems were analysed separately, only daily RM was associated with a significant reduction in all-cause mortality (odds ratio 0.65, $P = 0.021$) (*Figure 2*). This suggests that specific features may play an important role for the impact of RM on clinical outcomes and that the results from one RM system may not necessarily extend to another.[19]

A later meta-analysis by Klersy *et al.*,[20] including three additional RCTs, confirmed no significant effect of RM on mortality [relative risk (RR) 0.90, $P = 0.41$], cardiac mortality (RR 0.93, $P = 0.80$), or cardiac hospitalization (RR 0.96, $P = 0.60$) in pooled data (*Tables 1* and *2*). Their analysis did not separate results according to messaging philosophies.

Non-randomized large-scale registries

In contrast to RCTs, non-randomized studies with mega cohorts of (>100 000) patients treated with ICDs or CRT-Ds,[35,47,48] or medium cohorts (≈1000 patients),[49] have shown 45–50% reduction in mortality in the RM arm over up to 5 years of follow-up ($P = 0.002$ to $P < 0.0001$, using weekly or less frequent data transmission). The survival improvement was amplified with higher levels of RM utilization, indicating a 'dose-dependent' effect.[15,35] According to their non-randomized fashion, there are possible sources of bias in these

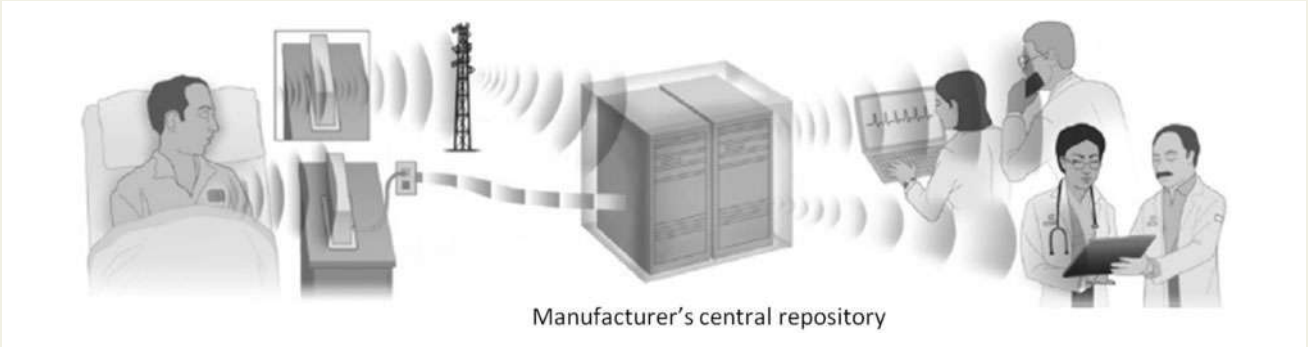

Figure 1 Illustration of the wireless remote monitoring technology for cardiovascular implantable electronic devices. The data transceiver is typically situated in the patient's bedroom, to receive data from the implant automatically during the night and relay them to the manufacturer's central repository using a mobile network link or a landline. Caregivers will receive automated e-mail, SMS, or fax alert notifications if pre-specified criteria are met and can view all transmitted data on a secure, dedicated website. Adapted from Slotwiner *et al.*[15] with permission of Elsevier.

Table 1 RCTs and meta-analyses contributing to the present all-cause mortality analysis

Study (Ref. #)	RM system	Sample size (*n*)	Mean age (years)	Mean LVEF[a] (%)	NYHA III (II, I) (%)	CRT-D[b] devices (%)	Average[c] follow-up (months)	Mortality for RM+IPE vs. IPE	
								HR (95% CI)[d]	RR (95% CI)[d]
RCTs of daily RM									
TRUST, 2010[5]	HM	1339	64	28.8	30 (57, 12)	0	12	NA	0.70 (0.40–1.22)[e]
ECOST, 2013[7]	HM	433	62	34.9	9 (62, 26)	0	24	NA	0.96 (0.52–1.78)[e]
IN-TIME, 2014[23]	HM	664	65	26	57 (43, 0)	59	12	0.36 (0.17–0.74) [*P = 0.004*]	0.37 (0.18–0.74)[e] [*P < 0.05*]
Osmera *et al.*, 2014[40]	HM	198	67	40	1.8 ± 0.9[f]	0	37	NA	1.08 (0.64–1.81)[e]
EuroEco, 2015[41]	HM	303	62	39.4	NA	0	22	NA	1.21 (0.51–2.86)[e]
[g]IMPACT, 2015[42]	HM	2718	64	29.7	36 (54, 9)	36	24	1.07 (0.85–1.34)	NA
MONITOR-ICD, 2017[43]	HM	402	63	35	NA	0	19	1.34 (0.68–2.61)	NA
RCTs of other systems									
Al-Khatib *et al.*, 2010[16]	CLN	151	63[h]	26.5[h]	3 (78, 20)	18	12	NA	1.32 (0.30–5.85)[e]
CONNECT, 2011[6]	HM	1997	65	28.9	48 (40, 10)	NA	15	NA	1.04 (0.72–1.48)[e]
EVOLVO, 2012[18]	CLN[i]	200	68[h]	30.5[h]	19 (69, 12)	91	16	NA	0.89 (0.32–2.46)[e]
MORE-CARE Phase 2, 2016[22]	CLN[i]	865	67	27.4	62 (38, 0)	100	24	1.13 (0.71–1.80)	NA
OptiLink HF, 2016[21]	OV (+CLN)	1002	66	26.7	81 (19, 0)	63	23	0.89 (0.62–1.28)	NA
REM-HF, 2017[34]	CLN[i], LAT, MER	1650	69	30.0	31 (69, 0)	54[j]	33	0.83 (0.66–1.05)	NA
Meta-analyses									
Parthiban *et al.*, 2015[19]	HM, CLN	4932[k]	65	29	NA	NA	≈14.4[l]	NA	0.83 (0.58–1.17)[m]
Klersy *et al.*, 2016[20]	HM, CLN	5433[n]	65[h]	29.5[h]	III–IV: 40	NA	≈15.7[l]	NA	0.90 (0.69–1.16)
Truecoin, 2017[44]	HM	2405°	64	29	34 (54, 11)	16	12[p]	NA	0.62 (0.40–0.95) [*P = 0.037*]

[a]Values are provided with as many decimal points as in the original publications.
[b]Otherwise ICD devices.
[c]Mean or median, whatever provided in the original publication.
[d]Values from the original publications, unless stated otherwise. In case of statistical significance, the published *P*-value is indicated in italics and square brackets.
[e]Calculated in a meta-analysis by Klersy *et al.*[20]
[f]Published only as mean ± standard deviation.
[g]Included for the overview completeness, but excluded from mortality analysis in *Figure 3* for two reasons: (i) HM was used also in the control arm, except for data on atrial tachyarrhythmia; and (ii) the intervention arm basically tested an experimental therapy schema for atrial tachyarrhythmia that was reasonable but not guideline-conform, i.e., had no proven efficacy.
[i]OptiVol alerts enabled.
[h]Median value.
[j]The only study including also CRT-P without defibrillator (13%). The use of ICD was 33%.
[k]Including seven RCTs: TRUST, ECOST, IN-TIME, Al-Khatib *et al.*, CONNECT, EVOLVO, and MORE-CARE Phase 1.[45]
[l]We calculated the value based on the number of patients and average follow-up duration in the individual studies.
[m]Odds ratio rather than RR.
[n]Including nine RCTs: TRUST, ECOST, IN-TIME, Osmera *et al.*, EuroEco, Al-Khatib *et al.*, CONNECT, EVOLVO, and MORE-CARE Phase 1.[45]
°An individual patient data meta-analysis of TRUST, ECOST, and IN-TIME with respect to mortality, and of ECOST and IN-TIME with respect to the mechanism of HM benefit based on adjudicated events.
[p]Limited to 12 months by Truecoin study design.
Study acronyms: CONNECT, Clinical Evaluation of Remote Notifications to Reduce Time to Clinical Decision; ECOST, Effectiveness and Cost of ICDs Follow-up Schedule with Telecardiology; EVOLVO, Evolution of Management Strategies of Heart Failure Patients with Implantable Defibrillators; EuroEco, European Health Economic Trial on Home Monitoring in Implantable Cardioverter-Defibrillator Patients; IMPACT, Multicenter Randomized Trial of Anticoagulation Guided by Remote Rhythm Monitoring in Patients with Implanted Cardioverter-Defibrillator and Resynchronization Devices; IN-TIME, Influence of Home Monitoring on Mortality and Morbidity in Heart Failure Patients with Impaired Left Ventricular Function; MONITOR-ICD, Randomized Comparison of Economic and Clinical Effects of Automatic Remote Monitoring versus Control in Patients with Implantable Cardioverter-Defibrillators; MORE-CARE, Monitoring Resynchronization Devices and Cardiac Patients; OptiLink, Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink; REM-HF, Remote Management of Heart Failure Using Implantable Electronic Devices; Truecoin, TRUst+ECOst+INtime; TRUST, Lumos-T Safely Reduces Routine Office Device Follow-up.
CI, confidence interval; CLN, CareLink Network (Medtronic Inc.; Minneapolis and Tempe, USA); CRT-D, cardiac resynchronization therapy defibrillator; HM, Home Monitoring (Biotronik SE & Co. KG; Berlin, Germany); HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IPE, in-person evaluation; LAT, Latitude Patient Management System (Boston Scientific; St Paul, USA); LVEF, left ventricular ejection fraction; MER, Merlin.net (St. Jude Medical; Sylmar, USA); NA, not available; NYHA, New York Heart Association class; OV, OptiVol (pulmonary congestion) algorithm; RCT, randomized controlled trial; RM, remote monitoring; RR, relative risk.

Table 2 Primary endpoint, CV mortality, and CV hospitalization in studies from *Table 1*

Study	Primary endpoint		CV mortality[a]	CV hospitalization[a]	Significant difference
	Definition	Result[a]			
RCTs of daily RM					
TRUST	(1) Efficacy: number of total in-hospital device evaluations; (2) Safety: adverse event rate (death, stroke, or surgical intervention)	(1) 2.1 vs. 3.8 ppy, $P < 0.001$; (2) 10.4% vs. 10.4% (non-inferiority $P < 0.05$, i.e., no difference)	[b]RR: 0.61, CI: 0.23–1.52	NA	Efficacy primary endpoint (no hard clinical outcome involved)
ECOST	Proportion of patients with ≥1 major adverse event (death, CV-related, procedure-related, or device-related)	HR: 0.91, $P = 0.53$, CI: 0.68–1.23	[b]RR: 1.06, CI: 0.45–2.48	NA	–
IN-TIME	Worsened composite score of death, WHF hospitalization, change in NYHA, and patient global self-assessment	OR: 0.63, $P = 0.013$, CI: 0.43–0.90	HR: 0.37, $P = 0.012$, CI: 0.16–0.83	[c]RR: 0.93, CI: 0.62–1.40	Primary endpoint, death, CV death
Osmera *et al.*	Non-specific ('benefits of remote monitoring')	NA	NA	[c]RR: 0.99, CI: 0.54–1.83	–
EuroEco	Total follow-up related cost for providers during the first 2 years	P = non-significant	NA	[c]RR: 0.79, CI: 0.61–1.02	–
IMPACT	Composite of stroke, systemic embolism, and major bleeding	HR: 1.06, $P = 0.732$, CI: 0.75–1.51	P = non-significant	NA	–
MONITOR-ICD	Total disease-specific costs	P = non-significant	NA	NA	–
RCTs of other systems					
Al-Khatib *et al.*	Composite of CV hospitalization, emergency room visit for a cardiac cause, and unscheduled visit for a device-related issue	32% vs. 34%, $P = 0.77$	NA	[c]RR: 0.93, CI: 0.48–1.81	–
CONNECT	Time from device detection of a clinical event to a decision being made in response to the event	Median 4.6 vs. 22.0 days, $P < 0.001$	NA	[c]RR: 1.08, CI: 0.96–1.22	Primary endpoint (no hard clinical outcome involved)
EVOLVO	Rate of emergency department or urgent in-office visits for WHF, arrhythmias, or device-related events	IRR: 0.65, $P = 0.005$, CI: 0.49–0.88	NA	[c]RR: 1.19, CI: 0.81–1.74	Primary endpoint
MORE-CARE	Composite of death, CV hospitalization, and device-related hospitalization	HR: 1.02, $P = 0.89$, CI: 0.80–1.30	8.2% vs. 7.8%, $P = 0.87$	HR: 0.96, $P = 0.80$, CI: 0.73–1.28	–
OptiLink HF	Composite of death and CV hospitalization	HR: 0.87, $P = 0.13$, CI: 0.72–1.04	HR: 0.89, $P = 0.57$ CI: 0.58–1.34	HR: 0.89,$P = 0.22$, CI: 0.73–1.08	–
REM-HF	Composite of death and CV hospitalization	HR: 1.01, $P = 0.87$, CI: 0.87–1.18	HR: 0.88, $P = 0.34$, CI: 0.68–1.14	HR: 1.07,$P = 0.42$, CI: 0.91–1.25	–
Meta-analyses					
Parthiban *et al.*	NA	NA	[d]OR: 0.66, $P = 0.103$, CI: 0.41–1.09	NA	–
Klersy *et al.*	NA	NA	[e]RR: 0.93, $P = 0.474$, CI: 0.51–1.69	[f]RR: 0.96, $P = 0.188$, CI: 0.82–1.12	–

Continued

Table 2 *Continued*

Study	Primary endpoint		CV mortality[a]	CV hospitalization[a]	Significant difference
	Definition	Result[a]			
Truecoin	NA	NA	[g]ARD: −1.8%, $P = 0.11$, CI: −4.1% to 0.4%	NA (alternatively, CV hospitalization or CV death: [g]ARD: −3.3%, $P = 0.22$, CI: −8.7% to 2.0%;WHF hospitalization or WHF death: [g]ARD: −4.6%, $P = 0.020$, CI: −8.4% to 0.7%)	Death, WHF hospitalization, or WHF death

[a]Values and formats (e.g. HR with CI, or HR with *P*-value, or only *P*-value, etc.) are shown as in original publications, unless stated otherwise. Significant *P*- and CI values for difference between groups are underlined.
[b]Defined as cardiac mortality, calculated by Klersy *et al.*[20]
[c]Defined as cardiac hospitalization, calculated by Klersy *et al.*[20]
[d]Including four trials: TRUST, ECOST, IN-TIME, and MORE-CARE Phase 1.[45]
[e]Defined as 'cardiac' rather than CV. Including three trials: TRUST, ECOST, and MORE-CARE Phase 1.[45]
[f]Defined as 'cardiac'. Including eight trials: IN-TIME, Osmera, EuroEco, Al-Khatib, CONNECT, EVOLVO, MORE-CARE Phase 1,[45] and SAVE-HM (contributed to CV hospitalization only, narrowly missing significance in favour of RM (RR: 0.30; CI: 0.09–1.01).[46]
[g]Including two trials: ECOST and IN-TIME.
Study acronyms: CONNECT, Clinical Evaluation of Remote Notifications to Reduce Time to Clinical Decision; ECOST, Effectiveness and Cost of ICDs Follow-up Schedule with Telecardiology; EVOLVO, Evolution of Management Strategies of Heart Failure Patients with Implantable Defibrillators; EuroEco, European Health Economic Trial on Home Monitoring in Implantable Cardioverter-Defibrillator Patients; IMPACT, Multicenter Randomized Trial of Anticoagulation Guided by Remote Rhythm Monitoring in Patients with Implanted Cardioverter-Defibrillator and Resynchronization Devices; IN-TIME, Influence of Home Monitoring on Mortality and Morbidity in Heart Failure Patients with Impaired Left Ventricular Function; MONITOR-ICD, Randomized Comparison of Economic and Clinical Effects of Automatic Remote Monitoring versus Control in Patients with Implantable Cardioverter-Defibrillators; MORE-CARE, Monitoring Resynchronization Devices and Cardiac Patients; OptiLink, Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink; REM-HF, Remote Management of Heart Failure Using Implantable Electronic Devices; Truecoin, TRUst+ECOst+INtime; TRUST, Lumos-T Safely Reduces Routine Office Device Follow-up.
ARD, absolute risk difference; CI, confidence interval; CV, cardiovascular; HR, hazard ratio for RM+IPE vs. IPE; IPE, in-person evaluation; IRR, incident rate ratio; NA, not available or not applicable; NYHA, New York Heart Association class; OR, odds ratio for RM+IPE vs. IPE; ppy, per patient-year; RCT, randomized controlled trial; RM, remote monitoring; RR, relative risk for RM+IPE vs. IPE; WHF, worsening heart failure.

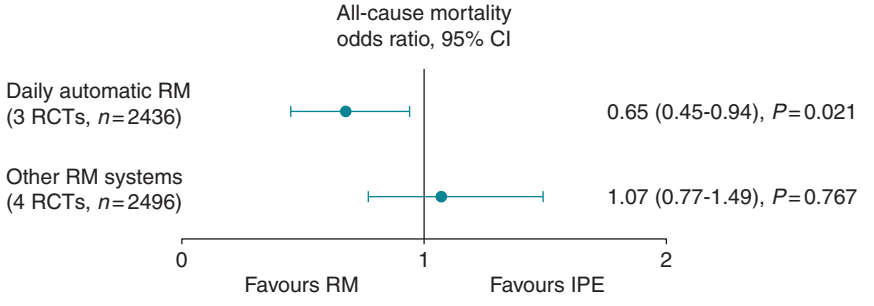

Figure 2 Comparison of RM with daily data transmission and RM with basically weekly data transmission, vs. IPE alone. The indicated odds ratios, 95% CIs, and *P*-values are taken from the text of Parthiban *et al.*[19] Data are presented here visually without additional calculations. Baseline characteristics of the 2436 patients in three trials of daily RM (TRUST,[5] ECOST,[7] and IN-TIME[23]) and 2496 patients in four other trials (Al-Khatib *et al.*,[16] CONNECT,[6] EVOLVO,[18] and MORE-CARE phase 1[45]) were similar regarding the mean age (64 vs. 65 years), mean left ventricular ejection fraction (29% vs. 29%), proportion of ischaemic cardiomyopathy (67% vs. 60%), and follow-up duration (15 vs. 15 months), respectively. CI, confidence interval; IPE, in-person evaluation; RCT, randomized controlled trial; RM, remote monitoring.

studies, such as a lower likelihood for sicker patients to receive or activate RM option, even though they are more likely to benefit from RM, because of the preference for in-office encounters.[50] Considering the huge number of patients analysed and that survival benefit was observed even in low-risk populations, such as pacemaker patients, also other factors may be responsible for the results.[35,50] For example, RM technology with frequent transmissions may inspire patients to become more aware of, and in touch with, their health status and involved in their care, potentially improving clinical outcomes.

Recent randomized trials

Published meta-analyses to date have not included three recent RCTs (MORE-CARE, OptiLink HF, and REM-HF) in which data were routinely transmitted in intervals of seven or more days, combined with additional specific alerts.

MORE-CARE randomized 865 CRT-D patients to RM with automated alerts for fluid overload by means of intrathoracic impedance, for atrial tachyarrhythmia, and for system integrity, or to IPE alone (*Table 1*).[22] The primary endpoint, the composite of death, CV hospitalization, and device-related hospitalization, did not differ significantly between the arms after 2 years of follow-up (HR 1.02, $P = 0.89$). Similarly, the individual endpoint components of all-cause mortality (HR 1.13, $P = 0.59$), CV hospitalization (HR 0.96, $P = 0.80$), and device-related hospitalization (HR 0.89, $P = 0.74$), were not different (*Tables 1* and *2*).

In the OptiLink HF trial, 1002 patients with advanced HF implanted with an ICD (37%) or a CRT-D (63%) were randomly allocated to periodical RM interrogation with daily check of alerts for fluid overload, or to no RM.[21] Apart from a slightly worse New York Heart Association (NYHA) status, baseline characteristics were similar to MORE-CARE (*Table 1*). Fluid alerts triggered a protocol-specified algorithm to guide symptom assessment and treatment initiation. No significant difference was found concerning the combined primary endpoint of all-cause death and CV hospitalization (HR 0.87, $P = 0.13$) or its individual components: all-cause mortality (HR 0.89, $P = 0.52$) and CV hospitalization (HR 0.89, $P = 0.22$) over 2 years of follow-up. The same was true for CV mortality (HR 0.89, $P = 0.57$) and worsening HF (WHF) hospitalization (HR 0.87, $P = 0.28$).[21] The authors concluded that impedance based fluid alerts for pulmonary congestion did not significantly improve outcomes in ICD/CRT-D patients with advanced HF. In the accompanying editorial, Hindricks and Varma[37] noted that the patient population was appropriate and almost identical to that in IN-TIME, yet the results significantly differed, since IN-TIME demonstrated positive findings for RM.

While devices applied in both MORE-CARE and OptiLink HF trials used intrathoracic impedance monitoring, a feature proposed to provide early warning of impending fluid overload in HF patients,[51] such measurement was not included in IN-TIME. Clinical utility of impedance monitoring is supported by retrospective data,[52–54] but prospective data have failed to confirm benefit.[21,22,55] A range of factors has been proposed to explain inefficacy of impedance monitoring such as alert transmission failures (connectivity weaknesses),[21] low adherence to clinical alert pathways,[21,37] and insufficient diagnostic performance of the fluid detection algorithm.[37,56–59] Still, it appears reasonable to keep impedance as a part of multiparameter approach in selected patients with a high risk of volume overload and in the setting of a dedicated heart team.[54]

The third study, REM-HF, randomized 1650 patients with predominantly mild HF symptoms (NYHA class II, 70%) to weekly RM or 'Usual care' for 3 years (*Table 1*).[34] Three different proprietary systems were utilized, but none programmed to daily transmissions. A minor portion of cardiac resynchronization therapy pacemakers (CRT-Ps, 13%) was included beside ICD (33%) and CRT-D (54%) devices. Though remote device control was part of 'Usual care' in a part of patients, this was not likely to bias outcome since remote control was performed every 6 months at its most frequent and not used to manage HF in any form. No significant differences were found in either the primary endpoint, a composite of death and unplanned CV hospitalization (HR 1.01, $P = 0.87$), or in the individual components of all-cause mortality (HR 0.83, $P = 0.12$), CV hospitalization (HR 1.07, $P = 0.42$), or CV mortality (HR 0.88, $P = 0.34$) (*Tables 1* and *2*).[34] In a subgroup analysis, device type and essential patient characteristics did not interact with the overall neutral result. It was concluded that in developed healthcare systems with high quality HF services, using data from weekly RM of CIEDs is unlikely to improve patient outcomes.[34,60]

Regarding daily RM technology, after TRUST,[5] ECOST,[7] and IN-TIME,[23] there have been no pivotal RCTs focusing on outcomes of patients with advanced HF; rather, cost-effectiveness and atrial fibrillation (AF) management have been in the first plan (*Tables 1* and *2*).

Daily remote monitoring: Truecoin and comparisons with REM-HF

To better understand the mechanism by which daily RM reduced all-cause and CV mortality in IN-TIME, Hindricks *et al.*[44] recently performed an individual patient meta-analysis (Truecoin) of three Home Monitoring trials: TRUST, ECOST, and IN-TIME (*Table 1*). The composite CV endpoints combining CV- or all-cause mortality and CV hospitalization, and the composite WHF endpoints combining WHF- or all-cause mortality and WHF hospitalization were analysed. It was found that the benefit of daily RM was largely driven by the prevention of WHF events (*Table 2*).[44] This suggests that patients with more severe HF may gain a greater clinical benefit of RM. We further analysed the relationship between HF severity and RM effectiveness in *Figure 3*, which relates the mean left ventricular ejection fraction (LVEF) to mortality benefit in trials of daily RM. As seen, a beneficial effect of RM on survival is more likely in patients with more depressed LVEF, who generally have a high mortality risk.

A key finding in IN-TIME was that AF detection was the main reason for clinicians to contact patients based on RM findings, and that patients with pre-existing AF particularly benefited from RM.[23] Although the value of early AF detection to guide decisions on anticoagulation treatment is still undetermined,[42] AF may increase the risk of inappropriate ICD shocks and reduce the percentage of biventricular pacing, thus adversely influencing HF status and prognosis.[56,61] Atrial fibrillation may also be associated with fluid overload, and therefore, serve as a risk indicator of upcoming HF

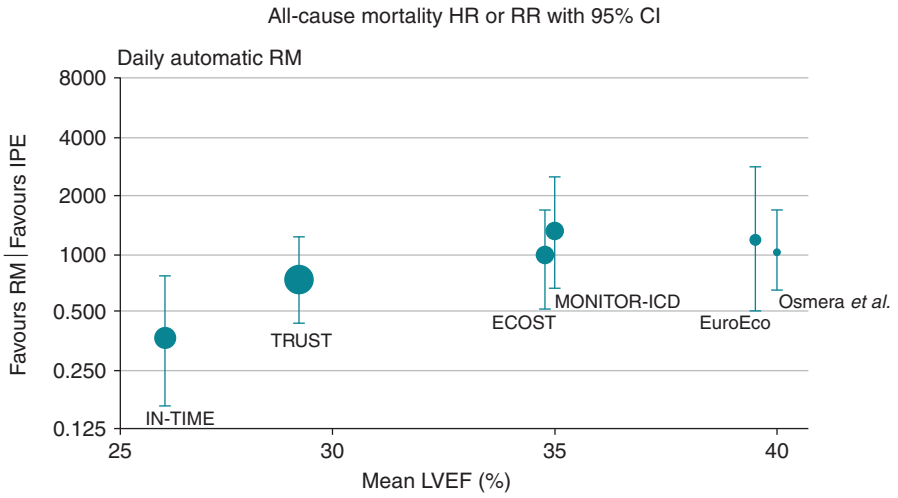

Figure 3 Scatter diagram of all-cause mortality HR or RR (whatever available in *Table 1*), for RM+IPE vs. IPE alone, as a function of mean LVEF—results from randomized controlled trials with daily RM. Study acronyms as in *Table 1*. Diameters of the circles are proportional to the number of randomized patients. Only IN-TIME observed a statistically significant reduction in mortality. CI, confidence interval; HR, hazard ratio; IPE, in-person evaluation; LVEF, left ventricular ejection fraction; RM, remote monitoring; RR, relative risk.

events.[61,62] In a recent trial (CASTLE-AF), AF ablation in selected HF patients with an ICD or CRT-D improved the combined endpoint of mortality and HF hospitalization.[63] Despite methodological limitations, CASTLE-AF findings underline the potential importance of maintaining sinus rhythm in selected patients with HF.[63]

To better understand why overall results differed between Truecoin and the REM-HF trial,[34] we compared operational details. Five major differences emerge: (i) Truecoin included only daily RM, while REM-HF excluded this approach; (ii) in REM-HF, there was no true control group with IPE alone, because control patients were permitted to continue with alert-based RM if this was already in place[60]; (iii) REM-HF required weekly RM transmissions to be actively performed by the patients and almost 40% of patients transmitted data for <75% of weeks[60]; this attrition in compliance degraded connectivity, i.e. the foundation for RM, in contrast to successful transmission on >85% of days in Truecoin consistently during follow-up.[8,9,23,31–33,39] (iv) REM-HF investigational sites were overloaded with unfiltered data—the nine sites received 79 325 RM transmissions over 2 years (10–15 transmissions/day per site); consequently, the attending physicians initiated medication change or advised the patient to seek medical attention in only 226 (<0.3%) and 910 (<1.2%) of transmissions, respectively[34,60]; (v) parameters followed were different, e.g. thoracic impedance was not used in IN-TIME but was included in REM-HF. These factors together represent fundamental differences between the two studies and may account for different results.

Guideline recommendations on remote monitoring

In the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure,[24] two RM concepts are recommended to improve clinical outcomes in HF patients: daily multiparameter RM as used in the IN-TIME trial and pulmonary artery pressure monitoring (a single-sensor method in a stand-alone device).

Daily multiparameter RM may be considered in symptomatic HF patients treated with ICDs/CRT-Ds, who have reduced LVEF despite optimal drug treatment.[24] This approach essentially involves an advanced clinical workflow with screening of RM data during office hours and, upon alerts, a structured interview on the patient's overall condition, weight change, and drug compliance, as in IN-TIME. A central monitoring unit composed of trained study nurses and supporting physicians reviewed monitoring data in order to ensure the investigators' awareness of RM events. Therapeutic decisions were at the treating physician's discretion and the monitoring unit may be functionally unnecessary if clinical attitude to telemonitoring is appropriate.[23] Apart from the specific technical features of different RM systems, the implementation of RM in the routine clinical work flow is of paramount importance to realize potential benefits of this approach, thus connecting the circle from device-based RM to advanced patient management.[64]

The second recommended approach in the guidelines, the implantable monitoring of pulmonary artery pressure,[65,66] may be used to reduce the risk of recurrent WHF hospitalization in symptomatic, previously hospitalized HF patients irrespective of the LVEF.[24] The recommendation was given based on the CHAMPION trial demonstrating a 33% reduction in WHF hospitalization in patients randomized to a pre-specified treatment guided by daily pulmonary artery pressure measurements vs. standard care ($P < 0.0001$).[24] Daily data transmission was, thus, a common feature of both recommended RM concepts.

In contrast, telemonitoring of body weight, blood pressure, and HF symptoms was associated with variable clinical results and is not explicitly recommended in the current guidelines.[24,30]

Patient contacts and physician reactions

In clinical practice, the translation of remotely transmitted data into appropriate clinical action still represents a major challenge requiring a paradigm shift from a patient-triggered medical service to proactive interventions based on changes or alerts from device-based monitoring.[61] The fully automatic RM system eliminates the need for patient participation in the transmission process and is not subject to compliance erosion. In IN-TIME, the use of a central monitoring unit in addition to frequent transmissions was instrumental in facilitating early treatment adjustments.[37] Interestingly, a comparable predefined and centralized workflow was applied in the CHAMPION trial that also yielded positive outcomes.[65,66] Certainly, the level of expertise provided by dedicated monitoring units, whether operated by a specialized remote provider or by well-trained personal in-house, will add to the quality of data interpretation and the effectiveness of subsequent clinical responses.

Overall, robust practice systems are necessary to ensure that patients remain connected to RM, which data are transmitted at the desired frequency, and that relevant findings are communicated to the patient and corresponding healthcare providers.[15] New complex concepts have been considered, in which monitoring will be tailored to individual phenotypes, for a personalized medicine approach, with possible progress from crisis detection to health maintenance with RM.[67]

Discussion

Follow-up of patients with CIEDs represents a challenge in clinical practice due to increasing patient numbers and medical complexity of their cases. RM offers an opportunity to improve follow-up efficiency by monitoring technical function and disease-specific parameters, in particular to modify the progression of HF which is a source of considerable patient morbidity and mortality and cost for health care. But the adoption of RM in clinical routine remains modest despite the Class 1 recommendation in an expert consensus statement,[15] even in health care systems incentivised to use RM.[10,56,61,68] Apart from the reimbursement issue, reasons for the halting uptake include the need for significant changes in the workflow of CIED clinics[15] and the paucity of evidence that RM improves relevant CV outcomes.

In this review, we have tried to identify the components of a remote management strategy of patients with ICDs or CRT-Ds that may improve outcome. Firstly, selection of patients likely to gain most—we show here that high-risk HF patients with a markedly suppressed systolic left ventricular function have the highest propensity of gaining a survival benefit. Probably, close monitoring and early interventions (also for AF) have influenced the clinical course and translated into reduced WHF events (Truecoin[44]) with improved prognosis.

Secondly, transmission philosophy matters, since it affects level of connectivity. Daily RM ('high-intensity RM') was shown to have advantage in two separate proprietary platforms.[23,65,66] However, only a 'head-to-head' comparison between daily RM and other systems could provide direct evidence in support of this superiority. Thirdly, the parameters monitored (the 'right' parameters) affect efficacy. The multiparameter approach (without impedance) in IN-TIME and the pulmonary artery pressure sensor in CHAMPION were effective. The addition of a dedicated haemodynamic sensor to the multiparameter approach might, however, further improve its effectiveness.

Finally, a well-designed response system to device mediated alerts is of great importance. This may include a central monitoring unit, but essentially requires well-defined algorithms directing the evaluation of patient status and adjustment of medical therapy to provide timely efficacious clinical response mechanisms.[15,37] These factors are all interconnected, and their coordination in a remote management plan appears critical to ensure success.[23] Enabling all this remains dependent on reimbursement and other incentives to improve the awareness and adherence of clinicians to RM.

Conclusion

RM is recommended to implement an individualized and alert-driven follow-up of CIED patients. Yet, further advances are warranted to translate the potential advantages of RM into improved patient outcomes, particularly concerning the management of patients with HF implanted with implantable cardioverter-defibrillators and resynchronization devices. Important components to achieve this goal include a higher level of connectivity enabling "high-intensity RM" and a well-designed clinical response system facilitating an effective management of actionable events. Furthermore, the optimal choice of sensors as part of a multiparameter approach and the appropriate selection of patients most likely to benefit from RM are critical to accomplish a significant impact of RM on patient outcomes.

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