



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

Frieder Braunschweig^{1*}, Stefan D. Anker², Jochen Proff³, and Niraj Varma⁴

¹Heart and Vascular Theme, Karolinska University Hospital, 17176 Stockholm, Sweden; ²Department of Cardiology and Pneumology, Innovative Clinical Trials, University Medical Centre Göttingen, Göttingen, Germany; ³Biotronik SE & Co. KG, Berlin, Germany; and ⁴Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA

Received 10 August 2018; editorial decision 15 January 2019; accepted 24 January 2019; online publish-ahead-of-print 21 March 2019

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

* Corresponding author. Tel: +46 8 51770000; fax: +46-8-311044. E-mail address: frieder.braunschweig@karolinska.se

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

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) (%)	CRFD ^b devices (%)	Average ^c follow-up (months)	Mortality for RM+IPE vs. IPE HR (95% CI) ^d	RR (95% CI) ^e
RCTs of daily RM									
TRUST, 2010 ⁵	HIM	1339	64	28.8	30 (57, 12)	0	12	NA	0.70 (0.40–1.22) ^e
ECOST, 2013 ⁷	HIM	433	62	34.9	9 (62, 26)	0	24	NA	0.96 (0.52–1.78) ^e
IN-TIME, 2014 ²³	HIM	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	HIM	198	67	40	1.8 ± 0.9 ^f	0	37	NA	1.08 (0.64–1.81) ^e
EuroEco, 2015 ⁴¹	HIM	303	62	39.4	NA	0	22	NA	1.21 (0.51–2.86) ^e
^g IMPACT, 2015 ⁴²	HIM	2718	64	29.7	36 (54, 9)	36	24	1.07 (0.85–1.34)	NA
MONITOR-ICD, 2017 ¹³	HIM	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	HIM	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	HIM, CLN	4932 ^k	65	29	NA	NA	≈14.4 ^l	NA	0.83 (0.58–1.17) ^m
Klersy et al., 2016 ²⁰	HIM, 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	HIM	2405 ^o	64	29	34 (54, 11)	16	12 ^p	NA	0.62 (0.40–0.95) [P = 0.037]

^aValues are provided with as many decimal points as in the original publications.

^bOtherwise ICD devices.

^cMean or median, whatever provided in the original publication.

^dValues from the original publications, unless stated otherwise. In case of statistical significance, the published P-value is indicated in italics and square brackets.

^eCalculated in a meta-analysis by Klersy et al.²⁰

^fPublished only as mean ± standard deviation.

^gIncluding the overview completeness, but excluded from mortality analysis in Figure 3 for two reasons: (i) HIM 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.

^hOptiVol alerts enabled.

ⁱMedian value.

^jThe only study including also CRT-P without defibrillator (13%). The use of ICD was 33%.

^kIncluding seven RCTs: TRUST, ECOST, IN-TIME, Al-Khatib et al., CONNECT, EVOLVO, and MORE-CARE Phase 1.⁴⁵

^lWe calculated the value based on the number of patients and average follow-up duration in the individual studies.

^mOdds ratio rather than RR.

ⁿIncluding nine RCTs: TRUST, ECOST, IN-TIME, Osmera et al., EuroEco, Al-Khatib et al., CONNECT, EVOLVO, and MORE-CARE Phase 1.⁴⁵

^oAn 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.

^pLimited 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 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; HIM, 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 <i>et al.</i>	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 <i>et al.</i>	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 <i>et al.</i>	NA	NA	^d OR: 0.66, $P = 0.103$, CI: 0.41–1.09	NA	–
Klersy <i>et al.</i>	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	Result ^a	CV mortality ^a	CV hospitalization ^a	Significant difference
	Definition				
Truecoinc	NA	NA	[§] ARD: -1.8%, <i>P</i> = 0.11, CI: -4.1% to 0.4%	NA (alternatively, CV hospitalization or CV death: [§] ARD: -3.3%, <i>P</i> = 0.22, CI: -8.7% to 2.0%; WHF hospitalization or WHF death: [§] ARD: -4.6%, <u><i>P</i> = 0.020</u> , <u>CI: -8.4% to 0.7%</u>)	Death, WHF hospitalization, or WHF death

^aValues 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.

^bDefined as cardiac mortality, calculated by Klersy et al.²⁰

^cDefined as cardiac hospitalization, calculated by Klersy et al.²⁰

^dIncluding four trials: TRUST, ECOST, IN-TIME, and MORE-CARE Phase 1.⁴⁵

^eDefined as 'cardiac' rather than CV. Including three trials: TRUST, ECOST, and MORE-CARE Phase 1.⁴⁵

^fDefined 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

^gIncluding 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; Truecoinc, 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.

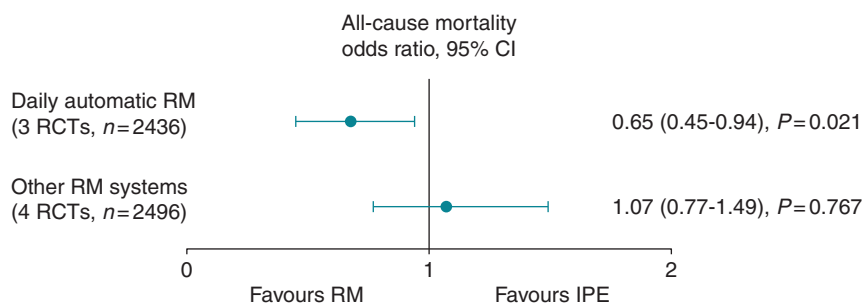


Figure 2 Comparison of RM with daily data transmission and RM with basically weekly data transmission, vs. IPE alone. The indicated odds ratios, 95% CIs, and *P*-values are taken from the text of Parthiban et al.¹⁹ Data are presented here visually without additional calculations. Baseline characteristics of the 2436 patients in three trials of daily RM (TRUST,⁵ ECOST,⁷ and IN-TIME²³) and 2496 patients in four other trials (Al-Khatib et al.,¹⁶ CONNECT,⁶ EVOLVO,¹⁸ and MORE-CARE phase 1⁴⁵) 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 Varma³⁷ 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

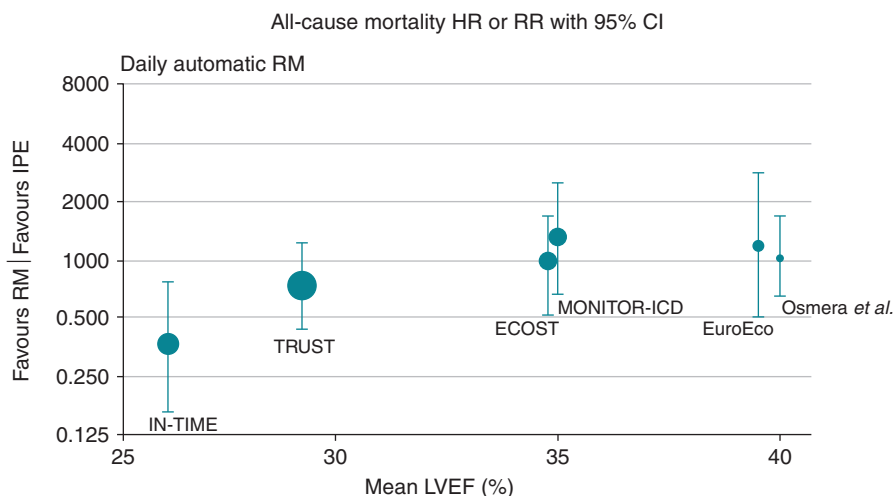


Figure 3 Scatter diagram of all-cause mortality HR or RR (whatever available in Table 1), for RM+IPE vs. IPE alone, as a function of mean LVEF—results from randomized controlled trials with daily RM. Study acronyms as in Table 1. Diameters of the circles are proportional to the number of randomized patients. 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 place⁶⁰; (iii) REM-HF required weekly RM transmissions to be actively performed by the patients and almost 40% of patients transmitted data for <75% of weeks⁶⁰; 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 pre-defined 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 clinics¹⁵ 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 (Truecoin⁴⁴) 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.

Acknowledgements

We thank Dejan Danilovic, PhD, for critical reading and editing of the manuscript.

Conflict of interest: F.B. received fees for consultancy by Medtronic and Biotronik. J.P. is an employee of Biotronik. S.D.A. reports grants from Vifor and Abbott Vascular, and fees for consultancy from Vifor, Bayer, Boehringer Ingelheim, Brahms, Janssen, Novartis, Servier and Stealth Peptides. N.V. reports previous consultancy for Biotronik.

References

1. Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM et al. HRS/EHRA Expert Consensus on the Monitoring of Cardiovascular Implantable Electronic Devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Europace* 2008;**10**:707–25.
2. Theuns DA, Res JC, Jordaens LJ. Home monitoring in ICD therapy: future perspectives. *Europace* 2003;**5**:139–42.
3. 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–S12.
4. Crossley GH, Chen J, Choucair W, Cohen TJ, Gohn DC, Johnson WB et al. Clinical benefits of remote versus transtelephonic monitoring of implanted pacemakers. *J Am Coll Cardiol* 2009;**54**:2012–9.
5. Varma N, Epstein AE, Irimpen A, Schweikert R, Love C. 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**:325–32.
6. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH. 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**:1181–9.

7. Guedon-Moreau L, Lacroix D, Sadoul N, Clementy J, Kouakam C, Hermida JS et al. A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial. *Eur Heart J* 2013;**34**: 605–14.
8. Varma N, Pavri BB, Stambler B, Michalski J. Same-day discovery of implantable cardioverter defibrillator dysfunction in the TRUST remote monitoring trial: influence of contrasting messaging systems. *Europace* 2013;**15**:697–703.
9. Hindricks G, Elsner C, Piorkowski C, Taborsky M, Geller JC, Schumacher B et al. 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.
10. Varma N, Ricci RP. Impact of remote monitoring on clinical outcomes. *J Cardiovasc Electrophysiol* 2015;**26**:1388–95.
11. Marzegalli M, Lunati M, Landolina M, Perego GB, Ricci RP, Guenzati G et al. Remote monitoring of CRT-ICD: the multicenter Italian CareLink evaluation—ease of use, acceptance, and organizational implications. *Pacing Clin Electrophysiol* 2008;**31**:1259–64.
12. Ricci RP, Morichelli L, Quarta L, Sassi A, Porfli A, Laudadio MT et al. Long-term patient acceptance of and satisfaction with implanted device remote monitoring. *Europace* 2010;**12**:674–9.
13. Petersen HH, Larsen MC, Nielsen OW, Kensing F, Svendsen JH. Patient satisfaction and suggestions for improvement of remote ICD monitoring. *J Interv Card Electrophysiol* 2012;**34**:317–24.
14. Varma N, Michalski J, Stambler B, Pavri BB. Superiority of automatic remote monitoring compared with in-person evaluation for scheduled ICD follow-up in the TRUST trial - testing execution of the recommendations. *Eur Heart J* 2014; **35**:1345–52.
15. Slotwiner D, Varma N, Akar JG, Annas G, Beardsall M, Fogel RI et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Heart Rhythm* 2015;**12**: e69–100.
16. 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**:545–50.
17. Varma N, Michalski J, Epstein AE, Schweikert R. Automatic remote monitoring of implantable cardioverter-defibrillator lead and generator performance: the Lumos-T Safely RedUceS RouTine Office Device Follow-Up (TRUST) trial. *Circ Arrhythm Electrophysiol* 2010;**3**:428–36.
18. Landolina M, Perego GB, Lunati M, Curnis A, Guenzati G, Vicentini A et al. 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**:2985–92.
19. Parthiban N, Esterman A, Mahajan R, Twomey DJ, Pathak RK, Lau DH et al. Remote monitoring of implantable cardioverter-defibrillators: a systematic review and meta-analysis of clinical outcomes. *J Am Coll Cardiol* 2015;**65**: 2591–600.
20. Klersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V et al. 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.
21. Bohm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C et al. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J* 2016;**37**:3154–63.
22. Boriani G, Da Costa A, Quesada A, Ricci RP, Favale S, Boscolo G et al. 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. *Eur J Heart Fail* 2017;**19**:416–25.
23. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–90.
24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
25. Jung W, Rillig A, Birkemeyer R, Miljak T, Meyerfeldt U. Advances in remote monitoring of implantable pacemakers, cardioverter defibrillators and cardiac resynchronization therapy systems. *J Interv Card Electrophysiol* 2008;**23**:73–85.
26. Burri H, Senouf D. Remote monitoring and follow-up of pacemakers and implantable cardioverter defibrillators. *Europace* 2009;**11**:701–9.
27. Dubner S, Auricchio A, Steinberg JS, Vardas P, Stone P, Brugada J et al. ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs). *Europace* 2012;**14**:278–93.
28. Nagele H, Lipoldova J, Oswald H, Klein G, Elvan A, Vestner E et al. Home monitoring of implantable cardioverter-defibrillators: interpatient reliability of the second-generation “IEGM Online” system. *Europace* 2015;**17**:584–90.
29. Braunschweig F, Ford I, Conraads V, Cowie MR, Jondeau G, Kautzner J et al. Can monitoring of intrathoracic impedance reduce morbidity and mortality in patients with chronic heart failure? Rationale and design of the Diagnostic Outcome Trial in Heart Failure (DOT-HF). *Eur J Heart Fail* 2008;**10**:907–16.
30. Al-Chekakie MO, Bao H, Jones PW, Stein KM, Marzec L, Varosy PD et al. Addition of blood pressure and weight transmissions to standard remote monitoring of implantable defibrillators and its association with mortality and rehospitalization. *Circ Cardiovasc Qual Outcomes* 2017;**10**:e003087.
31. Vogtmann T, Stiller S, Marek A, Kespohl S, Gomer M, Kuhlkamp V et al. Workload and usefulness of daily, centralized home monitoring for patients treated with CIEDs: results of the MoniC (Model Project Monitor Centre) prospective multicentre study. *Europace* 2013;**15**:219–26.
32. Perings SM, Perings C, Smetak N, Meyer C, Shin DI, Kelm M et al. Home Monitoring technology and integrated follow-up care of ICD patients. *Acta Cardiol* 2013;**68**:381–6.
33. Varma N, Love CJ, Schweikert R, Moll P, Michalski J, Epstein AE. Automatic remote monitoring utilizing daily transmissions: transmission reliability and implantable cardioverter defibrillator battery longevity in the TRUST trial. *Europace* 2018;**20**:622–8.
34. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J et al. Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**: 2352–60.
35. Varma N, Piccini JP, Snell J, Fischer A, Dalal N, Mittal S. Relationship between level of adherence to automatic wireless remote monitoring and survival in pacemaker and defibrillator patients. *J Am Coll Cardiol* 2015;**65**:2601–10.
36. Ploux S, Varma N, Strik M, Lazarus A, Bordachar P. Optimizing implantable cardioverter-defibrillator remote monitoring: a practical guide. *JACC Clin Electrophysiol* 2017;**3**:315–28.
37. Hindricks G, Varma N. Remote monitoring and heart failure: monitoring parameters, technology, and workflow. *Eur Heart J* 2016;**37**:3164–6.
38. Cronin EM, Ching EA, Varma N, Martin DO, Wilkoff BL, Lindsay BD. Remote monitoring of cardiovascular devices: a time and activity analysis. *Heart Rhythm* 2012;**9**:1947–51.
39. De Ruvo E, Sciarra L, Martino AM, Rebecchi M, Iulianella RV, Sebastiani F et al. A prospective comparison of remote monitoring systems in implantable cardiac defibrillators: potential effects of frequency of transmissions. *J Interv Card Electrophysiol* 2016;**45**:81–90.
40. Osmera O, Bulava A. The benefits of remote monitoring in long-term care for patients with implantable cardioverter-defibrillators. *Neuro Endocrinol Lett* 2014; **35**(Suppl 1):40–8.
41. Heidebuchel H, Hindricks G, Broadhurst P, Van Erven L, Fernandez-Lozano I, Rivero-Ayerza M et al. 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**:158–69.
42. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J* 2015;**36**:1660–8.
43. Zabel M, Willich SN, Geller JC, Brachmann J, Kuhlkamp V, Dissmann R et al. A randomized comparison of economic and clinical effects of automatic remote MONITORing versus control in patients with ICDs: the MONITOR-ICD study. *Heart Rhythm* 2017;**14**:S58 (abstract).
44. Hindricks G, Varma N, Kacet S, Lewalter T, Sogaard P, Guedon-Moreau L et al. Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST). *Eur Heart J* 2017;**38**:1749–55.
45. Boriani G, Da Costa A, Ricci RP, Quesada A, Favale S, Iacopino S et al. 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.
46. Perl S, Stiegler P, Rotman B, Prenner G, Lercher P, Anelli-Monti M et al. Socio-economic effects and cost saving potential of remote patient monitoring (SAVE-HM trial). *Int J Cardiol* 2013;**169**:402–7.
47. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTTITUDE survival study. *Circulation* 2010;**122**:2359–67.
48. Akar JG, Bao H, Jones PW, Wang Y, Varosy PD, Masoudi FA et al. Use of remote monitoring is associated with lower risk of adverse outcomes among patients with implanted cardiac defibrillators. *Circ Arrhythm Electrophysiol* 2015;**8**:1173–80.
49. De Simone A, Leoni L, Luzi M, Amellone C, Stabile G, La Rocca V et al. Remote monitoring improves outcome after ICD implantation: the clinical efficacy in the management of heart failure (EFFECT) study. *Europace* 2015;**17**:1267–75.

50. Akar JG, Bao H, Jones P, Wang Y, Chaudhry SI, Varosy P et al. Use of remote monitoring of newly implanted cardioverter-defibrillators: insights from the patient related determinants of ICD remote monitoring (PREDICT RM) study. *Circulation* 2013;**128**:2372–83.
51. Yu CM, Wang L, Chau E, Chan RH, Kong SL, Tang MO et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. *Circulation* 2005;**112**:841–8.
52. Whellan DJ, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB et al. 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**:1803–10.
53. Cowie MR, Sarkar S, Koehler J, Whellan DJ, Crossley GH, Tang WH et al. Development and validation of an integrated diagnostic algorithm derived from parameters monitored in implantable devices for identifying patients at risk for heart failure hospitalization in an ambulatory setting. *Eur Heart J* 2013;**34**:2472–80.
54. Gudmundsson K, Lynga P, Rosenqvist M, Braunschweig F. Monitoring of daily body weight and intrathoracic impedance in heart failure patients with a high risk of volume overload decompensation. *Clin Cardiol* 2016;**39**:446–52.
55. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G et al. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation* 2011;**124**:1719–26.
56. Bertini M, Marcantoni L, Toselli T, Ferrari R. Remote monitoring of implantable devices: should we continue to ignore it? *Int J Cardiol* 2016;**202**:368–77.
57. Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu CM et al. Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: the SENSE-HF trial. *Eur Heart J* 2011;**32**:2266–73.
58. Ono M, Varma N. Remote monitoring to Improve long-term prognosis in heart failure patients with implantable cardioverter-defibrillators. *Expert Rev Med Devices* 2017;**14**:335–42.
59. Ypenburg C, Bax JJ, van der Wall EE, Schalij MJ, van EL. Intrathoracic impedance monitoring to predict decompensated heart failure. *Am J Cardiol* 2007;**99**:554–7.
60. Burri H. Is there a future for remote cardiac implantable electronic device management? *Arrhythm Electrophysiol Rev* 2017;**6**:109.
61. Linde C, Braunschweig F. Cardiac resynchronization therapy follow-up: role of remote monitoring. *Card Electrophysiol Clin* 2015;**7**:797–807.
62. Andriulli JA, Moore HJ, Hettrick DA, Ousdigian KT, Johnson J, Markowitz SM. Atrial tachyarrhythmias temporally precede fluid accumulation in implantable device patients. *Pacing Clin Electrophysiol* 2014;**37**:554–61.
63. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L et al. Catheter ablation for atrial fibrillation with left ventricular dysfunction. *N Engl J Med* 2018;**378**:417–27.
64. Desai AS, Stevenson LW. Connecting the circle from home to heart-failure disease management. *N Engl J Med* 2010;**363**:2364–7.
65. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–66.
66. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;**387**:453–61.
67. Hawkins NM, Virani SA, Sperrin M, Buchan IE, McMurray JJ, Krahn AD. Predicting heart failure decompensation using cardiac implantable electronic devices: a review of practices and challenges. *Eur J Heart Fail* 2016;**18**:977–86.
68. Mairesse GH, Braunschweig F, Klersy K, Cowie MR, Leyva F. Implementation and reimbursement of remote monitoring for cardiac implantable electronic devices in Europe: a survey from the health economics committee of the European Heart Rhythm Association. *Europace* 2015;**17**:814–8.