

A current and future outlook on upcoming technologies in remote monitoring of patients with heart failure

Tarek Bekfani^{1*}, Marat Fudim², John G.F. Cleland³, Ana Jorbenadze⁴,
 Stephan von Haehling^{5,6}, Avraham Lorber⁷, Alexander M.K. Rothman⁸,
 Kenneth Stein⁹, William T. Abraham¹⁰, Horst Sievert^{11,12}, and Stefan D. Anker^{13,14}

¹Division of Cardiology, Angiology and Intensive Medical Care, Department of Internal Medicine I, University Hospital Magdeburg, Otto von Guericke-University, Magdeburg, Germany; ²Division of Cardiology, Duke University Medical Center, Durham, NC, USA; ³Robertson Centre for Biostatistics and Clinical Trials Unit, Institute of Health and Wellbeing, University of Glasgow and National Heart & Lung Institute, Imperial College, London, UK; ⁴Tbilisi Heart and Vascular Clinic, Tbilisi, Georgia; ⁵Department of Cardiology and Pneumology, University of Göttingen Medical Centre, Göttingen, Germany; ⁶German Centre for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany; ⁷Pi-Harvest Ziv Hospital, Safed, Israel; ⁸University of Sheffield and Sheffield Teaching Hospitals NHS Trust, Sheffield, UK; ⁹Boston Scientific, Marlborough, MA, USA; ¹⁰Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; ¹¹CardioVascular Center Frankfurt, Frankfurt, Germany; ¹²Anglia Ruskin University, Chelmsford, UK; ¹³Division of Cardiology and Metabolism – Heart Failure, Cachexia & Sarcopenia, Department of Cardiology, Campus Virchow-Klinikum, Charité – Medical School, Berlin, Germany; and ¹⁴Berlin-Brandenburg Centre for Regenerative Therapies (BCRT), Charité – Medical School Berlin, Berlin, Germany

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Heart failure is a major health and economic challenge in both developing and developed countries. Despite advances in pharmacological and device therapies for patients with a reduced left ventricular ejection fraction (LVEF) and heart failure, their quality of life and exercise capacity are often persistently impaired, morbidity and mortality remain high and the health economic and societal costs are considerable. For patients with heart failure and preserved LVEF, diuretic management has an essential role for controlling congestion and symptoms, even if no intervention has convincingly shown to reduce morbidity or mortality. Remote monitoring might improve care delivery and clinical outcomes for patients regardless of LVEF. A great variety of innovative remote monitoring technologies and algorithms are being introduced, including patient self-managed testing, wearable devices, technologies either integrated into established clinically indicated therapeutic devices, such as pacemakers and defibrillators, or as stand-alone are in development providing the promise of further improvements in service delivery and clinical outcomes. In this article, we will discuss unmet needs in the management of patients with heart failure, how remote monitoring might contribute to future solutions, and provide an overview of current and novel remote monitoring technologies.

Keywords Heart failure • Remote monitoring

Introduction

Heart failure (HF) is a major health, social and economic problem worldwide.¹ Incidence and prevalence are increasing,² in part due to an aging population and rising burden of comorbidities.³ Efforts to decrease mortality, reduce hospitalization rates and improve the well-being of patients with HF were modestly successful over the last decades in spite of the introduction of many effective medical therapies and care strategies.⁴ Indeed, HF readmission rates remain high and represent an increasingly unsustainable financial burden.⁵ In the U.S. alone, the costs

related to HF are expected to reach 70 billion U.S. dollars by 2030, an increase of 130% on current costs.^{6–8} The 30-day readmission rate as a key indicator of hospital performance is still with currently 25% high.^{9,10} As a result, reducing readmission rates has become a priority in many of the developed countries.^{11,12}

Adherence to guideline-directed medical therapy,¹³ the provision of an effective care plan to patients with advanced HF and an effective discharge planning performed by a multidisciplinary expert team are all purported to reduce hospitalization rates and health costs.^{14–16} Unfortunately, data from registries show that only a

*Corresponding author: Department of Cardiology, University Hospital Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany. Tel: +49 391 6713229, Fax: +49 391 6713202, Email: tarek.bekfani@med.ovgu.de

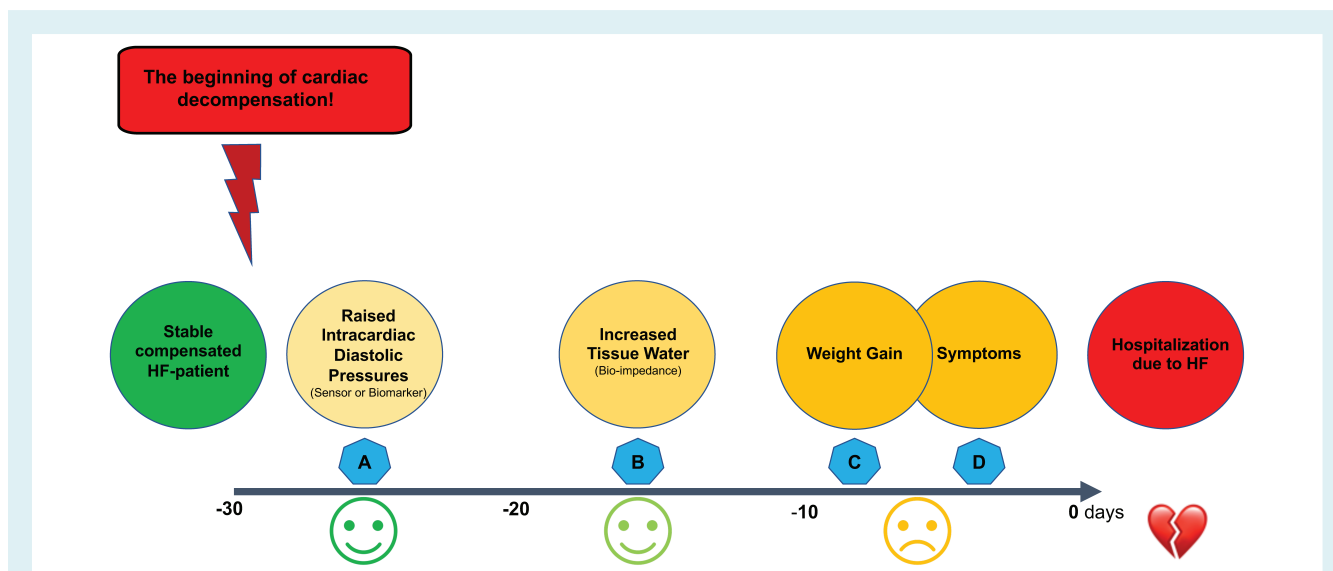


Figure 1 Phases of decompensated heart failure (HF). Currently, we tend to act when patients are in phase C. Ideally, we should react earlier when patients are still in phase A or B. Remote monitoring offers different possibilities in this regard. Modified from Adamson *et al.*¹⁸

small proportion of patients with HF achieve optimal doses of recommended HF therapy.^{17–20}

Understanding the pathophysiology of HF makes achieving and maintaining an euvoaemic status a key goal in the management of HF. As a response to the reduced cardiac output, the human body attempts to maintain an effective mean arterial pressure through a series of compensatory mechanisms. Over-activation of the sympathetic nervous system and renin–angiotensin–aldosterone system are among the earliest pathophysiological responses²¹ along with an increased metabolic rate driven by an active inflammatory process. Over the course of days to weeks, the body starts to retain salt and water. Paired with a decreased vascular compliance due to vasoconstriction, patients at this stage retain fluid, increase cardiac filling pressures, increase interstitial pulmonary fluid, and lastly increase weight.²²

Accordingly, a modified approach to patients with HF seems to be necessary. Historically clinicians tended to intervene at a later stage in the development of decompensation (phase C or D; *Figure 1*). However, based on monitoring of physiological variables that change early, meaningful clinical intervention might be necessary at an earlier phase (phase A or B) to control overt decompensation. It is estimated that earliest detectable changes in physiological measurements might occur 10–20 days prior to an onset of symptoms.¹⁸

As such, new means and technologies to improve monitoring of such parameters and care delivery are urgently required. Novel telemedicine technologies [also called remote monitoring (RM)] could represent a solution to the above-mentioned unmet needs in patients with HF in a manner similar to current practice in diabetes management through patients' education to improve adherence to lifestyle and medical therapies and to take a prompt action, when necessary. This should focus in the case of HF on adjusting the doses of diuretics.^{11,13} This is of special importance in

patients with HF with preserved ejection fraction that lack proven pharmacological treatments, and are susceptible to cardiac decompensations and mortality rates comparable to patients with HF with reduced ejection fraction.²³ Patients with HF with preserved ejection fraction were so far under-represented in many RM trials.

The utility of RM has become more apparent in the current state of a global COVID-19 pandemic, where social distancing is recommended and the number of in-person patient–physician contacts has dramatically declined.²⁴

Although the need and utility of RM appears intuitive, evidence to support the clinical benefit has been mixed, however. The reasons why some trials failed to show improvements in outcome may be diverse, due to patient selection, inadequate statistical power, insufficient sensitivity or specificity of the sensors or algorithms, failure by health professionals or patients to act on the information. In addition, the interpretation of the results of some trials may be unduly pessimistic. For instance, in Better Effectiveness After Transition–Heart Failure (BEAT-HF)²⁵, the improvement in quality of life (QoL) was greater with telemonitoring than observed in either with sacubitril/valsartan in the Prospective Comparison of ARNI [Angiotensin Receptor–Nepriylsin Inhibitor] with ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)²⁶ or dapagliflozin in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF).²⁷ Also, the absolute difference in mortality in BEAT-HF was larger at 6 months than for either of these much more highly powered pharmaceutical trials.²⁵ Availability, affordability, accessibility, and appropriateness are ideal characters of devices used in RM.²⁸

We will discuss in this review article the existing evidence of RM and its significance to address the unmet needs in HF management. The review reflects discussions among representatives from

academia, industry, and regulatory agencies at the Device-Heart Failure meeting (Paris, France, December 2019).

Results from recent landmark trials

The effectiveness of RM to improve life expectancy, QoL, and to reduce HF rehospitalizations has been demonstrated in several trials.^{29–31} In a recent Cochrane review, both non-invasive RM and structured telephone support have been shown to offer statistically and clinically meaningful benefits to patients with HF by reducing all-cause mortality.³² A meta-analysis of five trials evaluating the impact of haemodynamic-guided HF management in patients with symptomatic HF showed about 38% reduction in the risk for HF hospitalizations.³³ Table 1 summarizes the key studies conducted in the field of RM.^{25,29,31,34–39}

The Heart Failure Virtual Consultation (HFVC) is an internet-based video conference system that enables general practitioners, cardiologists and HF nurses to meet virtually. HFVC proved to be a powerful tool for the delivery of specialist care and the democratization of knowledge in the community.⁴⁰

The authors of the Trans-European Network-Home-Care Management System trial (TEN-HMS) investigated whether home telemonitoring (HTM) improves outcomes compared to nurse telephone support (NTS) and usual care for patients with HF who are at high risk of hospitalization or death. Patients were randomly assigned to HTM, NTS, or usual care in a 2:2:1 ratio. The primary endpoint was days lost as a result of death or hospitalization with NTS vs. HTM at 240 days. There was no statistically significant difference between the two groups. The number of admissions and mortality were similar among patients randomly assigned to NTS or HTM, but the mean duration of admissions was reduced by 6 days with HTM. Patients randomly assigned to receive usual care had higher 1-year mortality (45%) than patients assigned to receive NTS (27%) or HTM (29%) ($P = 0.032$).³⁴

In a sub-analysis of the TEN-HMS, the investigators tested the possibility of predicting hospitalization due to worsening HF using daily weight measurement. They concluded that many episodes of worsening HF are not necessarily associated with weight gain and therefore RM of weight alone may not have great value for HF management.⁴¹

Remote Management of Heart Failure Using Implantable Electronic Devices (REM-HF) is the largest prospective and randomized clinical trial conducted on RM with implanted devices. In this trial, 1650 patients with HF who had an implanted cardiac device were randomized to active weekly review of RM data or usual care across nine UK hospitals, with an average follow-up of 2.8 years. The primary outcome of death or hospitalization from cardiovascular causes was the same in the RM group (42.4%) and the control group (40.8%) of patients ($P = 0.87$), despite considerable extra activity being triggered by the remotely collected data.³⁸

The Influence of Home Monitoring on the Clinical Management of HF Patients with Impaired Left Ventricular Function study (IN-TIME) was a prospective randomized trial that analysed the benefit in clinical outcomes of RM of implanted devices. In this

study, 716 patients were recruited, and 664 patients were finally randomized to multiparameter RM in addition to standard of care or standard of care alone. The primary endpoint was a composite clinical score. This included all-cause death, HF hospitalization, change in New York Heart Association (NYHA) class, and change in patient global self-assessment. The composite clinical score was better in the RM population. Improvement in the composite outcome mainly resulted from a lower death rate in the RM group [estimated 1-year mortality 2.7% vs. 6.8%; hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.16–0.83; $P = 0.012$].³⁹

While there is no clear explanation for the difference in the results between REM-HF and IN-TIME, the results could be attributed to the weekly RM in REM-HF compared with the daily review and intervention in IN-TIME.

The effectiveness of RM after discharge of hospitalized patients with HF was investigated in the BEAT-HF trial, a clinical randomized trial conducted in six centres in California, USA. The follow-up period was in average 180 days. Centralized registered nurses conducted RM reviews, protocolized actions, and telephone calls. The primary outcome was readmission for any cause within 180 days after discharge. Secondary outcomes were all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and QoL at 30 and 180 days. At the end there was no reduction in 180-day readmissions among patients hospitalized for HF, in whom combined health coaching telephone calls and RM were performed.²⁵ Patients' adherence was a major limitation in this trial, given that only about 60% of patients were adherent for more than half of the time in the first 30 days.

The Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomized, controlled, multicentre trial, has shown promising results. Eligible patients with HF were randomized 1:1 to either RM + usual care or to usual care only. Patients were followed for 12 months. The primary outcome was the percentage of days lost due to unplanned cardiovascular hospitalizations or all-cause death per 100 person-year. The main secondary outcomes were all-cause and cardiovascular mortality. The investigators found that patients assigned to RM had fewer lost days compared with patients assigned to usual care. Cardiovascular mortality was not significantly different between the two groups.²⁹

The sub-study of TIM-HF2 investigated whether the biomarkers mid-regional pro-adrenomedullin (MR-proADM) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) could be used to identify low-risk patients unlikely to benefit from RM, thereby allowing more efficient allocation of the intervention. Both biomarkers were strongly associated with events. The primary endpoint of lost days increased from 1.0% (1.4%) in the lowest to 17.3% (17.6%) in the highest quintile of NT-proBNP (MR-proADM). The authors showed that biomarker guidance in the RM group would have saved about 150 h effort/year per 100 patients of the eligible population.³⁵

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial (CHAMPION) investigated the utility of wireless pulmonary artery (PA) haemodynamic monitoring in chronic HF in reducing HF hospitalization.³⁰ CardioMEMS™ is a small sensor placed in the PA. Readings can be taken (usually once daily) on the PA pressure

Table 1 Overview of important trials in remote monitoring in patients with heart failure

	No. of patients	Years conducted	Follow-up	Patients selection	Method of RM	Measured parameters	Primary endpoint	Primary endpoint met
TEN-HMS ⁴	426	Published 2005	240 days	- Recent admission of HF - LVEF <40%	HTM	Weight, blood pressure, heart rate and rhythm with automated devices linked to a cardiology centre	Days lost as a result of death or hospitalization with NTS vs. HTM at 240 days	+/-
BEAT-HF ²⁵	1437	2011–2013	180 days	- Currently HF hospitalization - Adults >50 years	Health coaching telephone calls and telemonitoring	Daily blood pressure, heart rate, symptoms, and weight	Readmission rate for any cause within 180 days after discharge	-
TIM-HF2 ^{29,35}	1571	2013–2017	12 months	- LVEF <45% or LVEF >45% and one diuretic in the permanent medical therapy - NYHA class II–III	Remote patient monitoring	Daily body weight, systolic and diastolic blood pressure, heart rate, analysis of the heart rhythm, peripheral capillary oxygen saturation and self-rated health status	The percentage of days lost due to unplanned cardiovascular hospitalizations or all-cause death per 100 person-year	+
CHAMPION ^{31,36,37}	550	2007–2009	6 months	NYHA class III	Wireless implanted MEMS-based PA pressure sensor	PA pressure	- Rate of HF-related hospitalizations - Freedom from device/system-related complications - Freedom from pressure sensor failure	+
REM-HF ³⁸	1650	2011–2014	2.8 years	NYHA class II–IV and implanted cardiac device (ICD, CRT-D/P)	Weekly data downloads from patients' devices with simultaneous review by remote monitors	ICD, CRT-D/P. Devices were used from multiple manufacturers (Medtronic, Boston Scientific, St. Jude Medical); bi-ventricular pacing %, nocturnal heart rate, thoracic impedance only in Medtronic and some St. Jude Medical devices, activity levels, AT/AF burden, ventricular arrhythmias, therapy from device, heart rate variability, lead integrity, device programming, V–V interval at time of D/L	Death or hospitalization from cardiovascular causes	-
IN-TIME ³⁹	716	2007–2013	12 months	- NYHA class II–III - LVEF <35% and implanted cardiac devices (ICD, CRT-D/P)	Automatic, daily, implant-based, multiparameter telemonitoring (onset of arrhythmias, duration of daily physical activities, ventricular ectopy, heart rate variability, mean heart rate in 24h, mean heart rate at rest)	ICD, CRT-D/P (Biotronik)	A composite clinical score consisting of all-cause death, HF hospitalization, change in NYHA class, and change in patient global self-assessment	+

AF, atrial fibrillation; AT, atrial tachycardia; CRT-D/P, cardiac resynchronization therapy-defibrillator/pacemaker; D/L, download; HF, heart failure; HTM, home telemonitoring; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NTS, nurse telephone support; NYHA, New York Heart Association; PA, pulmonary artery; RM, remote telemonitoring; V–V, interventricular.

basis. Patients were randomly assigned to management with a wireless implantable haemodynamic monitoring system (treatment group) or to a control group for at least 6 months. The investigators of the trial showed a reduction in hospitalization for patients who were managed with a wireless implantable haemodynamic monitoring system. Information about pulmonary arterial pressure in addition to clinical signs and symptoms resulted in improved HF management.^{31,36} The implantation of a wireless HF monitoring system (CardioMEMS™) in a real-world setting in patients with HF and NYHA class III symptoms has resulted in 80.4% reduction in HF admissions and 69% reduction in all-cause admissions.³⁰ The Hemodynamic-Guided Management of Heart Failure clinical trial is currently recruiting (GUIDE-HF, NCT03387813). The aim of this trial is to test the effectiveness of the CardioMEMS™ HF system in HF patients for whom there has been so far no indication for the use of this system, but who are at risk for future HF events or mortality (e.g. NYHA class II).

There are few published data on RM with CardioMEMS™ for patients with left ventricular assist devices (LVAD). In a retrospective analysis of 436 patients who had received a CardioMEMS™ device, 108 of whom also received an LVAD,⁴² the mean PA pressure at the time of CardioMEMS™ implantation was higher ($P < 0.001$) in the group that subsequently received an LVAD. Mean PA pressures decreased after LVAD implantation and remained stable for 1 year. The authors concluded that monitoring PA pressure may help decide the timing of LVAD implantation and in the monitoring of these patients.

In one meta-analysis, Zhu *et al.*⁴³ conducted a meta-analysis on 29 randomized clinical trials that included 10 981 patients followed for up to 36 months. In this analysis, telemonitoring included structured telephone support and interactive voice-response monitoring. Telemonitoring was associated with fewer hospitalizations, all-cause [odds ratio (OR) 0.82, 95% CI 0.73–0.91, $P = 0.0004$] and cardiac (OR 0.83, 95% CI 0.72–0.95; $P = 0.007$), and a lower all-cause mortality (OR 0.75, 95% CI 0.62–0.90; $P = 0.003$) with a similar effect on HF-related mortality (OR 0.84, 95% CI 0.61–1.16; $P = 0.28$) compared to conventional healthcare.⁴³

Novel and upcoming devices and technologies

We will summarize here the most recent and upcoming technologies as well as the evidence supporting RM in patients with HF (Table 2).

Implantable electronic devices

One of the longest established methods of RM is using the implantable cardiac devices to measure cardiopulmonary variables such as thoracic impedance (surrogate of lung fluid content), heart rate and heart rate variability.^{44,45} Ongoing efforts and novel technologies seek to improve detection algorithms of implanted devices and expand upon the success of the CardioMEMS™ implantable cardiopulmonary monitoring device.

HeartLogic™ algorithm

The HeartLogic algorithm was developed using data from the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients study (MultiSENSE).⁴⁶ The following sensor measurements were incorporated: heart sounds (S1, S3), lung impedance, respiratory rate and volume, activity, and night-time heart rate. The changes in sensors were weighted and aggregated based on a risk determination, resulting in a single composite index to alert clinicians when a patient's HF is worsening.

HeartLogic was found to augment baseline NT-proBNP assessment. Furthermore, a retrospective analysis indicated that the HeartLogic algorithm might be useful to detect gradual worsening of HF and to stratify risk of HF decompensation.^{46,47} Two studies seek to provide further evidence for clinical benefit:

- Multiple Cardiac Sensors for the Management of Heart Failure (MANAGE-HF) is a multicentre, global, prospective, open-label, multi-phase trial intended to evaluate the clinical efficacy of the HeartLogic HF diagnostic feature. This trial is currently enrolling (NCT03237858). Phase II of the MANAGE-HF trial will assess the clinical effectiveness of RM of HF patients with an implanted cardiac resynchronization therapy-defibrillator or implantable cardioverter-defibrillator that contain the HeartLogic feature against patients with RM but without HeartLogic alerts.
- The Precision Event Monitoring for Patients with Heart Failure using HeartLogic trial (PREEMPT-HF) is currently enrolling (NCT03579641). There are no primary safety and/or efficacy endpoints for this study. Subjects will be followed for about 12 months after baseline to observe the occurrence of clinical events. These are defined as the following: hospitalization (any cause), hospitalization due to HF, HF readmission 30 days after discharge, and HF outpatient visit where unscheduled intravenous diuretics are prescribed in a setting that does not involve patient admission (emergency department, outpatient clinic) (Table 2).

Heart failure risk status generated by cardiac implantable electronic device (TRIAGE-HF)

Heart failure risk status (HFRS) generated by cardiac implanted electronic devices was investigated in 100 patients with HF in three Canadian centres for up to 8 weeks (TRIAGE-HF, NCT01798797). Measurements included impedance/OptiVol (Medtronic Plc., MN, USA), patient activity, night heart rate, heart rate variability, percent CRT pacing, atrial tachycardia/atrial fibrillation, and episodes of untreated and device-treated arrhythmia. Patients with a high HFRS score were contacted by telephone to assess symptoms, and compliance with prescribed therapies, nutrition, and exercise. Clinician-assessed and HFRS-calculated risk were compared at study baseline and exit. Twenty-four high HFRS episodes were observed. Measurements associated with an increased risk of HF hospitalization included OptiVol index ($n = 20$), followed by low patient activity ($n = 18$) and elevated night heart rate ($n = 12$). High HFRS was associated with symptoms of worsening HF in 63% of cases ($n = 15$) increasing to 83% of cases ($n = 20$) when

Table 2 Overview of recent and future studies on remote monitoring in patients with heart failure

	No. of patients	Recruitment status	Patient selection	Method	Primary outcome measures
SMILE-HF (NCT02448342)	268	Terminated 2017	Patients with current hospitalization for ADHF, regardless of the LVEF	ReDS	The rate of recurrent events of HF readmissions
MANAGE-HF (NCT03237858)	2700 (estimated)	Completion estimated in January 2025	- Implanted ICD/CRT-D - NYHA class II–III	HeartLogic	- All-cause mortality - HF hospitalization
PREEMPT-HF (NCT03579641)	3750 (estimated)	Completion anticipated in January 2026	- Documented HF - ICD/CRT-D with HeartLogic	HeartLogic	To evaluate the association of HeartLogic sensors with 30-day HF readmission
TRIAGE-HF (NCT01798797)	100	Completed 2013–2015	Non-randomized, all subjects who have been implanted with an ICD or CRT-D for at least 3 months		- HFRS performance characterization from baseline until a subject completes 8 months of follow-up - Clinical signs and symptoms of worsening HF that are associated with an HFRS triggered by an OptiVol alert
CardioMEMS HF System OUS Post Market Study (NCT02954341)	800 (estimated)	Recruiting (2016–2023)	HF patients with NYHA class III who have experienced a HF hospitalization within the past 12 months	CardioMEMS	- Freedom from device/system-related complications - Freedom from pressure sensor failure - Annualized HF hospitalization rate at 1 year compared to the HF hospitalization rate in the year prior to enrolment
SIRONA-HF (NCT03375710)	10 (estimated)	Completion estimated in February 2021	NYHA class III	Cordella™	- Safety: freedom from adverse events - Efficacy: accuracy
PROACTIVE-HF (NCT04089059)	970 (estimated)	Completion estimated in May 2024	NYHA class III	Cordella™	- Mortality and HF hospitalizations or emergency department/hospital outpatient intravenous diuretic visits - Safety: device/system-related complications - Safety: pressure sensor failure
VECTOR-HF (NCT03775161)	30 (estimated)	Completion estimated in August 2021	NYHA class III, ambulatory class IV HF	V-LAP™	- Safety: device/system-related complications - Performance: accuracy
NANOSENSE (NCT03719079)	500 (estimated)	Completion estimated in December 2020	- At least 150 HF patients - The patient is either hospitalized with a primary diagnosis of acute or was discharged with a primary diagnosis of acute HF within 2 weeks prior to enrolment - NYHA class II–IV at time of enrolment	SimpleSENSE	To develop and validate a multi-parameter algorithm for the detection of HF prior to a HF event

ADHF, acute decompensated heart failure; CRT-D/P, cardiac resynchronization therapy-defibrillator/pacemaker; HF, heart failure; HFRS, heart failure risk status; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ReDS, remote electric sensing.

non-compliance with pharmacological therapies and lifestyle was considered. The authors concluded that HFRS might be a useful tool for RM of HF.⁴⁸

Implantable pulmonary artery pressure measurement (Cordella™)

In addition to the previously described CardioMEMS™, still the only Food and Drug Administration-approved pressure measurement device, other modalities are being currently tested. The Cordella™ system provides a comprehensive health status of the patient at home. The gathered data can be then shared with healthcare providers for further evaluation and management. The Cordella sensor integrates PA pressure data into the Cordella system to proactively deliver the information necessary to improve patient care between office visits.

The Evaluating the Safety and Efficacy of the Cordella™ Heart Failure System NYHA Class III Heart Failure Patients trial (SIRONA, NCT03375710) is a prospective, multicentre, open-label, single-arm clinical trial. Cordella™ is a PA pressure sensor. The primary safety endpoint was freedom from adverse events associated with the use of the Cordella™ HF system through 30 days post-implant. The primary efficacy endpoint was the accuracy of Cordella™ Sensor PA pressure measurements relative to standard-of-care fluid-filled catheter pressure measurements obtained by standard right heart catheterization at 90 days post-sensor implant. The primary results of the first-in-human SIRONA study are promising.⁴⁹ A further Prospective, Multicentre, Randomized, Controlled, Single-Blind Clinical Trial Evaluating the Safety and Efficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III Heart Failure Patients (PROACTIVE-HF) has just started recruiting. The study is expected to be completed in May 2024 (NCT04089059).

Left atrial haemodynamic monitoring system

An alternative to PA pressure monitoring is left atrial pressure monitoring.⁵⁰ The ongoing Left Atrium Monitoring System for Patients With Chronic Systolic & Diastolic Congestive Heart Failure trial (VECTOR-HF, NCT03775161) studies the safety and reliability of the V-LAP™ device in patients with HF irrespective of LVEF. V-LAP™ is a wireless, battery-free microcomputer, placed directly on the inter-atrial septum. The first device has been implanted in February 2019. Altogether 30 patients are planned to be included in six European centres across Germany, Israel, Italy, and England. The trial is estimated to be completed in August 2021.

Non-invasive-monitoring

Non-invasive monitoring for HF spans cardiac and extra-cardiac variables in an attempt to detect signs of cardiac decompensation.

Lung fluid volume and lung impedance measurement

Some studies have focused on non-invasive lung impedance-guided treatment in patients with HF (Impedance-HF) and showed

reduced mortality and reduced hospitalization rates due to acute HF.⁵¹ In addition, the extent of change in pulmonary fluid content using lung impedance-based therapy during HF hospitalization has been shown to be strongly predictive of HF readmission and event-free survival.⁵²

Remote dielectric sensing (ReDS™) is one example of a non-invasive technology used in the field of RM that contains clinical algorithms and performs an absolute measurement of lung fluid volume by using a focused electromagnetic radar beam through the right lung. Normal lung measures 20–35% lung fluid content (default target range). The measurement can be done without any skin contact in up to 45 s. Uriel *et al.*⁵³ showed using ReDS™ strong correlations in both tissue-measured fluid content and haemodynamic measurements with pulmonary artery wedge pressure. In this study, receiver operating characteristic analysis of the ability to identify a pulmonary artery wedge pressure ≥ 18 mmHg resulted in a ReDS cutoff value of 34%, with an area under the curve of 0.85, a sensitivity of 90.7%, and a specificity of 77.1%. Overall, ReDS <34% carries a high negative predictive value of 94.9%.

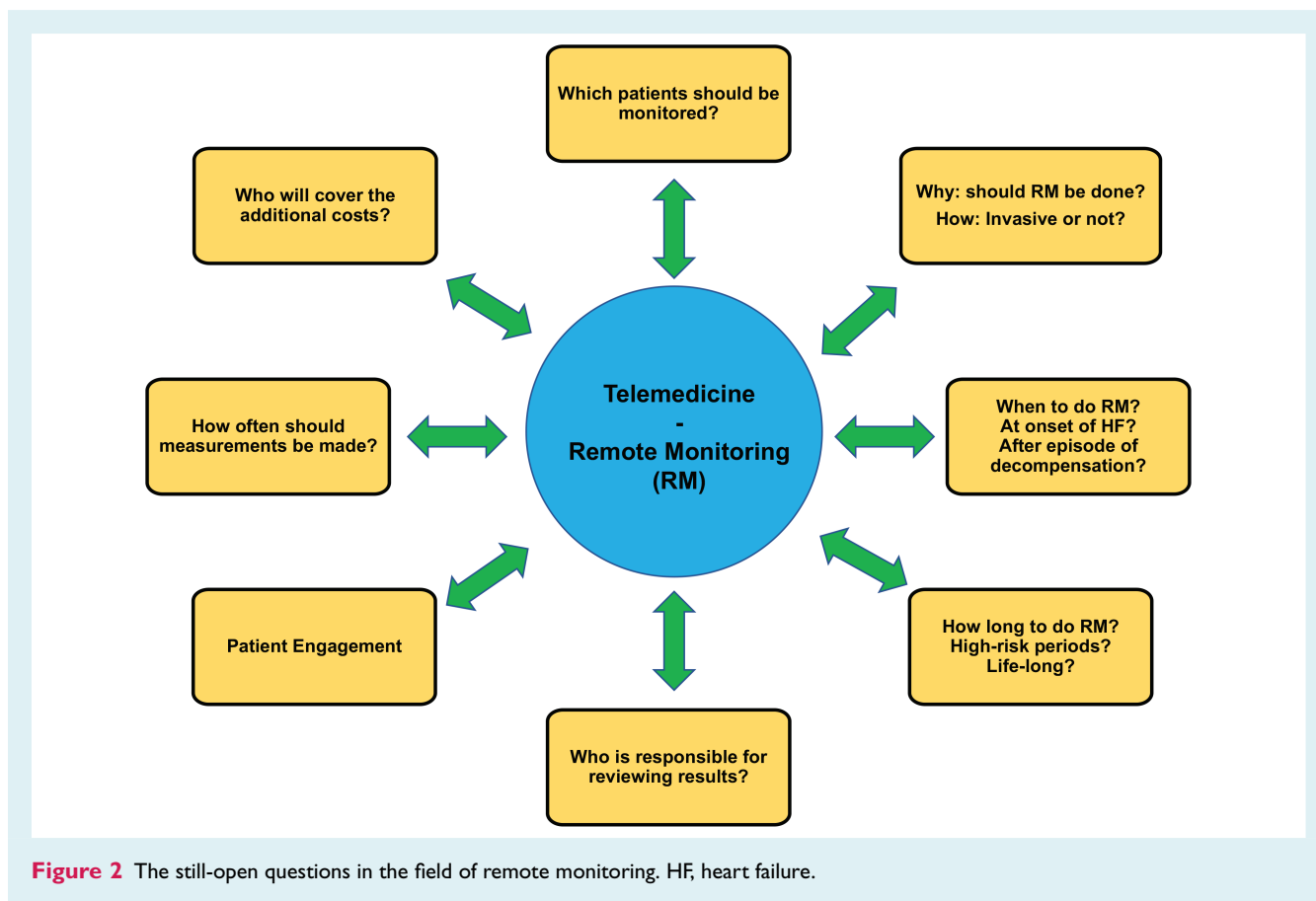
In the Evaluation Study of Remote Dielectric Sensing (ReDS) Technology-Guided Therapy for Decreasing Heart Failure Re-Hospitalizations, the investigators concluded that ReDS-guided management has the potential to reduce HF readmissions in acute HF patients recently discharged from the hospital.⁵⁴ The results of the SMILE trial were presented at the Heart Failure Society of America meeting 2019.⁵⁵ The study recruited 268 patients from 43 centres across the United States. The pre-specified endpoint of per-protocol changes in HF readmission was reduced in the ReDS™ treatment-guided HF management arm (HR 0.52, 95% CI 0.31–0.87; $P = 0.01$), which equates to a 48% readmissions reduction.

Non-invasive intracardiac pressure monitoring

A novel method of intracardiac pressure monitoring uses a non-invasive portable ultrasound-based measurement system. The new system is based on the image time series processing estimating the changes of the oscillating traceable regions via the introduction of the new ultrasound generalized M-mode and the notion of the derived image. The non-invasive system requires an initial calibration with simultaneous invasive pressure measurements, yet efforts are underway to eliminate this step using machine learning technology. The system has been successfully tested in animals (sheep).⁵⁶ Human validation trials were performed on 32 patients and a multicentre multinational study is pending. The intended in-home use will require the self-use of a portable ultrasound system by patients.

Heart failure diagnostics using wearable devices and technologies

There is currently a heightened focus on wearable monitoring technology both for detecting atrial fibrillation or for preventing hospitalization due to decompensated HF by observing early changes occurring before overt acute HF takes place.^{57,58}



Wearable health devices are part of digital and mobile health and represent potential instruments to improve HF care and outcomes. DeVore et al.⁵⁹ described this topic nicely in a recently published review article. Available data are currently limited to observational studies or small clinical randomized trials. Wearables are being integrated into HF trials as an intervention to assess outcomes. This may include lifestyle, pharmacological, device and mHealth interventions.⁶⁰ Future wearables of HF can be applied externally and include skin patches, watches and contact lenses and may monitor lactate or electrolytes.⁶¹

The Nanowear Wearable Heart Failure Management System Multiple Sensor Algorithm Development and Validation Trial is a multicentre prospective, non-randomized, observational study (NCT03719079). The aim is to enrol up to 500 subjects in order to collect data which include at least 150 HF hospitalizations in participating subjects. The trial is expected to be completed in December 2020. The study device is the Wearable Congestive Heart Failure Management System (VCHFS, also known as SimpleSENSE).

The observational multicentre study titled Evaluating Mobile Health Tool Use for Capturing Patient-Centered Outcomes Measures in HF Patients (NCT04191356) will evaluate the feasibility of a novel mobile health monitoring platform. Enrolment will start in 2020: 170 patients with HF are planned to be enrolled, and for 8 weeks the platform will capture patient-centred outcome measures. The primary outcome is the correlation between physiology

and accelerometer data collected from Everion and Apple Watch (i.e. heart rate, single-lead electrocardiogram report) with 6-min walk test, laboratory (i.e. estimated glomerular filtration rate, troponin, creatinine, NT-proBNP) results, and QoL measured using the Kansas City Cardiomyopathy Questionnaire-12 item and the 5-dimensions and 5-level European QoL (EQ-5D-5L) questionnaire.

These small feasibility studies may improve understanding of the technology but do not address the core issue of whether what can be done should be done. Only randomized controlled trials will help determine the clinical and financial effectiveness of RM.

More studies and evidence are required before a routine integration of these new technologies in the daily routine work-up or screening of patients with HF would become feasible. The future will show if wearable technologies will prove themselves to be an effective means in the field of RM and the management of patients with HF. How wearable technologies can complement implanted technology and in what instances they can replace the more invasive technology have yet to be determined.⁶²

Several questions remain open, however, and need to be answered: Which patients should be monitored? It seems to be reasonable to apply RM primarily to symptomatic patients (NYHA class III–IV), who suffer from cardiac decompensation in spite of guideline-directed medical therapy. The best time frame to start RM would be pre-discharge or shortly after that.³³ The chance of

these patients to decompensate again is much higher than those with stable HF and the heightened risk might justify the costs resulting from applying RM in this group of patients. In addition, the method of RM is still to be chosen. For example, devices with multiple sensors might be superior to single sensor method. Further issues should address the responsibility for reviewing the transmitted data and the frequency of the transmission and review of these data. Data should be transmitted securely to a medical centre. It is expected that medical personnel will receive a large volume of data that needs to be processed and analysed. Approving and paying for the additional costs resulting from RM is still an open question. An analysis based on the CHAMPION trial suggested that monitoring using the CardioMEMS™ device was cost-effective from a U.S. payer perspective, with the incremental cost to deliver one additional quality-adjusted life-year of approximately \$30 000 in the USA.³⁷ Unanswered questions in the field of RM are summarized in Figure 2. Additional clinical investigations will help to confirm and extend the existing evidence presented above and help to answer some of the questions raised.

Conclusion

Remote monitoring is a promising way to monitor and manage patients with HF (*graphical abstract*). RM could be performed non-invasively, through wearable devices, or by using developed algorithms integrated in implanted cardiac devices or invasively through continuous measuring of PA pressure. RM has been shown to improve the management and outcomes in patients with HF, but results do not apply to all technologies in all settings. Upcoming devices and technologies are being currently evaluated. Early results are promising. Questions regarding patient selection, timing of initiation and duration, and the most appropriate RM technology for each patient remain open. Further larger, randomized studies are required to refine our current knowledge and optimize patient care.

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