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Remote monitoring of heart failure: benefits for therapeutic decision making

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ABSTRACT

Introduction: Chronic heart failure is a cardiovascular disorder with high prevalence and incidence worldwide. The course of heart failure is characterized by periods of stability and instability. Decompensation of heart failure is associated with frequent and prolonged hospitalizations and it worsens the prognosis for the disease and increases cardiovascular mortality among affected patients. It is therefore important to monitor these patients carefully to reveal changes in their condition. Remote monitoring has been designed to facilitate an early detection of adverse events and to minimize regular follow-up visits for heart failure patients. Several new devices have been developed and introduced to the daily practice of cardiology departments worldwide.

Areas covered: Currently, special tools and techniques are available to perform remote monitoring. Concurrently there are a number of modern cardiac implantable electronic devices that incorporate a remote monitoring function. All the techniques that have a remote monitoring function are discussed in this paper in detail. All the major studies on this subject have been selected for review of the recent data on remote monitoring of HF patients and demonstrate the role of remote monitoring in the therapeutic decision making for heart failure patients.

Expert commentary: Remote monitoring represents a novel intensified follow-up strategy of heart failure management. Overall, theoretically, remote monitoring may play a crucial role in the early detection of heart failure progression and may improve the outcome of patients.

1. Introduction

Chronic heart failure (HF) is a cardiovascular disorder with high prevalence and incidence worldwide. The course of HF is characterized by periods of stability and instability. Deterioration of HF is associated with frequent and prolonged hospitalizations and it worsens the prognosis for the disease and increases cardiovascular mortality among affected patients. Globally deaths from cardiovascular disease have increased by 41% in the period from 1990 to 2013, while age-specific death rates decreased by 39% [1]. The age-standardized death rate per 100,000 for heart disease decreased from 520.4 to 169.1 (67.5% reduction; 95% CI, 67.4–67.6%) between 1969 and 2013 in the United States [2]. HF affects approximately 1–2% of the adult population worldwide [3–7]. The incidence of HF remains stable worldwide while the prevalence has increased over the recent decades [8,9]. Despite the current approach to the early diagnosis and treatment HF mortality remains high, especially in the developing countries [10–12]. Another important aspect is a high rate of HF-related admissions and readmissions and subsequent financial expenditures [13–19]. The high rate of readmission among HF patients associated with decompensation of the disease is due to a poor adherence to medical therapy, volume overload, natural course of disease, etc. The management of HF patients undergoing standard care includes scheduled office visits,

scheduled follow-ups and readmissions due to decompensation. Intensive follow-up by means of remote monitoring is currently presented by structured telephone support, telemedicine, remote monitoring with implanted therapeutic and monitoring-only devices. Remote monitoring systems prevent potential unfavorable cardiovascular events among HF patients.

The aim of this article is to review the recent data on remote monitoring of HF patients and present the role of remote monitoring in the therapeutic decision-making for HF patients.

2. Heart failure and device therapy

The European Society of Cardiology (ESC) guidelines defines HF as a 'a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress' [3]. High prevalence, poor quality of life, high risk of disability, poor prognosis, high rate of hospitalizations and readmissions and high level of associated financial cost make HF a significant public health problem [20].

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In the Framingham study, the incidence of HF was reported between 1.4 and 2.3 per 1000/year among persons aged 29 to 79 years [21]. The prevalence of HF highly depends on the applied definition and screening methods. According to the recent ESC guidelines for the diagnosis and treatment of acute and chronic HF it's classified into HF with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) [3]. The prevalence of HF among the adult population of developed countries is approximately 1–2% and ≥10% among people >70 years old [4–7]. Meantime, the prevalence of unrecognized HF is high among >65 years old population [22]. It has been demonstrated in Olmsted County that the age- and sex-adjusted incidence of HF decreased from 315.8 per 100,000 in 2000 to 219.3 per 100,000 in 2010 (37.5% rate reduction) [23].

Despite the current approach to the early diagnosis and treatment of HF (i.e. optimal medical therapy (OMT), device therapy), the prognosis of HF remains poor, though, the incidence and mortality of HF have decreased in western, developed countries. A 40% reduction of the age-standardized death rates due to HF has been demonstrated by Laribi et al. in seven European countries (Germany, Greece, England and Wales, Spain, France, Finland, and Sweden) in the period from 1987 to 2008 [24]. Between 2000 and 2009, the US age-standardized death rate from HF has decreased by 13.5% [25].

Despite the demonstrated decline the risk of sudden cardiac death (SCD) is still high among HF patients, which is mostly associated with a pump failure and malignant ventricular tachyarrhythmias [10]. Poor outcome of HF patients was demonstrated in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) study in 1987 [11]. Important studies around the millennium, such as the Framingham Heart Study and ARIC study, have demonstrated that an estimated survival of HF patients after being diagnosed is 50% and 10% at 5 and 10 years [12,26–30]. Severe left ventricular systolic dysfunction is a SCD risk factor among HF patients [31]. The median survival was 4.2 years among outpatients in the Henry Ford Health system [32].

The course of HF runs with periods of a stability and decompensation. Poor adherence to medical therapy, inadequate medical therapy, changes in diet, poor self-care and inadequate patient support, as well as the natural course of the disease are the main factors responsible for decompensation of HF. Factors, such a volume overload and persistent high filling pressures usually accelerate the natural course of disease [33]. Decompensation of HF often requires an intensification of treatment, readmission and prolonged in hospital treatment. HF is still the leading cause of hospitalization among adults >65 years of age in the USA [15]. HF is responsible for more than 1 million hospitalizations per year in the USA, which accounts for approximately $17 billion of expenditure [34]. Approximately 70% of HF related costs are due to hospitalization [35]. Hence, HF is considered as a significant socioeconomic problem, partly due to a substantial direct and indirect related cost (i.e. $30, and $33 billion respectively in 2006 and 2007 in the USA) [13,14]. The readmission rate among HF patients remains high and it is the highest within the first 6 months after an admission due to HF [16–18], approximately 24% of discharged patients is readmitted within 30 days due to HF decompensation [19].

3. Remote monitoring in heart failure: rationale

HF decompensation worsens the prognosis for the disease and increases cardiovascular mortality among affected patients. Besides, readmissions are associated with substantial financial cost. Hence, efforts should be made to accomplish the early detection of HF progression and the possible prevention of life-threatening conditions by timely intervention and appropriate management of the patients' treatment. Possible early prediction and prevention of HF decompensation may play a crucial role in improving the overall survival rate among HF patients, a reduction of readmission rates and substantial saving on costs associated with inhospital treatment, costly interventions and lead to an improvement of quality of care [36].

Recent guidelines recommend a multidisciplinary care approach to the management of HF patients [3,37]. The multidisciplinary HF care approach includes a standard care (i.e. inperson follow-up visits) and alternative approaches, most of which have been presented recently (i.e. regularly scheduled structured telephone contact between patient and health care specialist (i.e. trained nurse practitioner, physician), electronic transfer of physiological data using remote access technology via external, wearable, or implantable electronic devices [38]. These alternative approaches may potentially provide remote disease management by continuous or frequent assessment of some HF related physiological parameters. It may decrease the number of office visits and increase the efficiency of treatment through early detection and timely management of worsening HF.

The number of HF patients with implanted cardiac implantable electronic devices (CIEDs) has increased dramatically in recent decades [20,39]. A substantial number of modern CIEDs incorporate remote monitoring capability, which allows specialists to follow patients and access valuable cardiac data and alert messages from the device while the patient is at home. Simultaneously, the number of lead-related complications (i.e. lead failure) has increased because of the growing number of implantations, greater use of CIEDs in young patients, patients with more comorbidities, and an increase in device and procedure complexity [40]. Remote monitoring systems incorporated in CIEDs may have a potential positive role in the early diagnosis of lead-related complications before the scheduled office visit or scheduled device follow-up [41]. Another potential advantage of remote monitoring systems is an early detection of silent episodes of atrial fibrillation (AF), because of the strong association between AF and the risk of developing HF, increased mortality risk, and increased risk of thromboembolic (TE) events. The potential harmful effects of unrecognized AF in patients receiving cardiac resynchronization therapy (CRT), such as inappropriate shocks and impairment of CRT therapy, have also been demonstrated [42–48].

In summary, notwithstanding the current approach to the treatment of HF the rate of decompensation and subsequent readmission remains high. Meantime, despite a substantial improvement over time, survival after the diagnosis of HF remains poor. Remote monitoring which is currently available in the most of developed and developing countries may play an important role in prevention of HF decompensation.

Currently, remote monitoring of HF encompasses structured trans-telephonic support, telemonitoring, electronic transfer of physiological data from implanted therapeutic devices and implanted monitoring-only devices.

4. Remote monitoring of heart failure: tools and results

4.1. Structured trans-telephonic support and telemonitoring of HF patients

Structured telephone support and telemonitoring may become an alternative to the frequent office visits. Structured telephone support is a telephone consultation between the patient and physician or a trained nurse. The patient's symptoms and body weight play an important role in the decision-making based on the structured telephone support. In the systematic review of Inglis et al. 41 randomized clinical trials comparing structured telephone support (25 studies, 9332 patients) and telemonitoring (18 studies, 3860 patients) with standard care for HF were studied [49]. Telemonitoring was associated with a significant reduction in all-cause mortality (RR 0.80, 95% CI 0.68–0.94; participants = 3740; studies = 17; I^2 = 24%, GRADE: moderate-quality evidence) and HF-related hospitalizations (RR 0.71, 95% CI 0.60–0.83; participants = 2148; studies = 8; I^2 = 20%, GRADE: moderate-quality evidence). Structured telephone support showed decreased all-cause mortality (RR 0.87, 95% CI 0.77–0.98; participants = 9222; studies = 22; I^2 = 0%, GRADE: moderate-quality evidence) and HF-related hospitalizations (RR 0.85, 95% CI 0.77–0.93; participants = 7030; studies = 16; I^2 = 27%, GRADE: moderate-quality evidence) (Table 1). Neither structured telephone support nor telemonitoring demonstrated effectiveness in reducing the risk of all-cause hospitalizations (structured telephone support: RR 0.95, 95% CI 0.90–1.00; participants = 7216; studies = 16; I^2 = 47%, GRADE: very low-quality evidence; noninvasive telemonitoring: RR 0.95, 95% CI 0.89–1.01; participants = 3332; studies = 13; I^2 = 71%, GRADE: very low-quality evidence). In the Tele-HF study (Telemonitoring to Improve Heart Failure Outcomes) 1653 patients were included and randomized to telemonitoring care (826 patients) or standard care (827 patients) groups [50]. Readmission rates and deaths did not significantly differ between these two groups. Telemonitoring involved an interactive voice-response system that transmitted daily information about symptoms and weight to the clinicians. Only 55% of patients included in the telemonitoring group used the system at least three times per week by the end of the study, and 14% of patients never used the system. A total of 710 patients with stable HF were included and randomized to telemedical care (354 patients) or standard care (356 patients) groups in the TIM-HF study (Telemedical Interventional Monitoring in Heart Failure) [51]. Portable devices transferred encrypted data including electrocardiography, blood pressure and body weight via cell phones to the specialized telemedical centers. There were no significant differences in HF hospitalization among these two groups at a mean of 26 months on follow-up (hazard ratio (HR), 0.89; 95% CI, 0.67–1.19; P = .44).

Controversial results of clinical trials have been published regarding the remote management (i.e. telemedicine) in HF patients. Some other meta-analyses suggest clinical benefit, but several prospective clinical trials, such as Tele-HF, TIM-HF, INH, WISH and TEHAF have not confirmed it [50–54]. Hence, different telemedicine approaches have to be assessed on their individual merit.

4.2. Remote monitoring with implanted therapeutic devices

The number of HF patients with CIEDs has increased in recent decades [39]. A substantial number of modern CIEDs are equipped with remote monitoring capabilities. Remote monitoring of implantable cardioverter defibrillators (ICD) and CRT devices allow wireless download and stored diagnostic information from device to an external transmitter and transfer to the manufacturer's database. The data can be made available to the clinician through a specific interface [55]. Many parameters can be remotely monitored with potential implications for the clinicians' decision-making. These include diagnosis of disease deterioration and prevention of acute decompensation. Furthermore, technical features of the devices (antitachycardia pacing, DC shock, ventricular pacing percentage) and so-called 'heart failure diagnostic' parameters, such as thoracic impedance, heart rate variability, presence of arrhythmias, patients' activity level, mean heart rate at rest and exertion, can also be remotely monitored.

4.3. Detection of heart rhythm disorders

Identification of cardiac rhythm disorders (such as AF, premature ventricular complexes, etc.) among HF patients is important in the patients' daily management and in the prevention of potential complications. The prevalence of AF among HF patients is about 13–27%. Early diagnosis and management of AF may prevent AF-associated complications and worsening of the HF course [56–60]. Clinically silent arrhythmias, particularly silent episodes of AF may be diagnosed and registered in patients with CIEDs. This is a major advantage to patients with implanted CIEDs over patients without continuous monitoring. In the ASSERT study 34.7% of the 2580 patients, without a prior history of AF, experienced an episode of newly detected AF with more than 6 min of duration (during 2.5 years of follow-up) [61]. In 30% of patients included in the TRENDS trial (1368 patients with no history of AF, no previous stroke/TIA, no warfarin or antiarrhythmic drug use) experienced an episode of a newly detected AF (i.e. an episode of AF lasting more than 5 min on any day of the study) [62]. Approximately 62% of these patients with newly detected episodes of AF had a CHADS2 score of more than 1. The association between device detected AF and the risk of stroke has also been demonstrated (Table 1). In the ancillary MOST trial episodes of AF with more than 5 min of duration have clinical significance [63]. Data analysis from the EVEREST and HomeCARE studies (560 patients) has shown that patients with newly detected AF and those with a prior history of AF had more chance of experiencing thromboembolic events than those without newly detected AF episodes [64].

Table 1. Major studies demonstrating the role of remote monitoring in management of heart failure.

Study	Number of patients included	Study protocol	Results
1. Structured trans-telephonic support and telemonitoring of HF patients			
Tele-HF study	1653 patients	Telemonitoring care (interactive voice-response system) vs. usual care	1. Readmission rates – NS 2. Deaths – NS
TIM-HF study	710 patients	Telemedical care (portable devices transferred encrypted data including electrocardiography, blood pressure and body weight vs. usual care	1. Hospitalization rates – NS
2. Remote monitoring with implanted therapeutic devices: detection of heart rhythm disorders			
ASSERT study	2580 patients	Patients with implanted CIEDs, 2.5 years of follow-up. Newly detected AF episodes (with more than 6 min of duration) were counted	Newly detected AF episode have been detected in 34.7% of the involved population
TRENDS trial	1368 patients	Patients with no history of AF were included. Newly detected AF episodes (with more than 5 min of duration) were counted	Newly detected AF episode have been detected in 30% of the involved population
TRUST trial	1339 patients	Remote monitoring vs. standard follow-up	AF detection occurred at 5.5 days in the remote monitoring group compared with 40 days in the standard follow-up group
CONNECT trial	1997 patients	Patients with implanted ICDs were involved	3 vs. 24 days interval between AF episodes detection and clinical response in the remote monitoring vs. standard follow-up groups
COMPAS trial	538 patients	Remote monitoring follow-up vs. standard care (18.3 months of follow-up)	1. 17.3% vs. 19.1% (P < .01 for non-inferiority) patients experienced at least one major adverse event (all-cause death, hospitalizations for device-related or cardiovascular events) in the remote monitoring group and standard care group, respectively 2. Hospitalizations for atrial arrhythmias (6 vs. 18) and strokes (2 vs. 8) were fewer (P < .05) 3. Number of interim ambulatory visits was 56% lower (P < .001) in the remote monitoring than the standard care group
3. Detection and management of system-related complications in patients with implanted CIEDs			
ECOST trial	40 patients	Patients with high-voltage leads were involved, with 22 ± 4 months of follow-up after implantation	Lead failure was registered in 7.5% of patients
4. Detection of heart failure worsening in hemodynamics			
SENSE-HF trial	501 patients	Intracardiac impedance-derived fluid index measurement	Low sensitivity and positive predictive value in the early period after implantation (6 months), though sensitivity improved within the first 6 months after implantation
DOT-HF study	335 patients	Patients with implanted CIEDs were involved and randomized to have information available to physicians and patients as an audible alert in case of preset threshold crossings (access arm) or not (control arm)	Routine monitoring of intrathoracic impedance was not associated with a better outcome and was associated with an increased likelihood of HF hospitalization
PARTNERS-HF trial	694 patients	Patients with implanted CRTDs were involved and followed-up for 11.7 ± 2 months	Reduced impedance (or increased fluid index) has been demonstrated to be the most sensitive parameter to predict HF hospitalizations
IN-TIME trial	664 patients	Patients with NYHA class II and III and implanted ICDs and CRTDs were enrolled and randomized to standard vs. remote monitoring (in response to telemonitoring observations the investigators did a standardized telephone interview to establish whether patient's overall condition or symptoms had worsened or not, whether there was a sudden increase in body weight (>2 kg within the preceding 3 days) or scheduled visit to family doctor) arms	1. 63 patients (18.9%) with worsened composite clinical score in the telemonitoring group vs. 90 patients (27.2%) in the control group (P = .013) 2. Mortality was lower in the telemonitoring group compared to the control group (n = 10 vs. 27) 3. No significant differences in hospitalization among these groups was demonstrated
REM-HF trial	1650 patients	Patients with implanted CIEDs (ICD, CRTP, and CRTD) with remote monitoring were enrolled in the study and randomized to usual care or remote monitoring, with 2.8 years of median follow-up. Management of patients with remote monitoring was based on the data healthcare professional has received on a weekly basis from the device. Patients in usual care group had a usual care from heart failure service and remote monitoring of the device (once per 3–6 months)	No significant differences in the primary (death from any cause or unplanned hospitalization for cardiovascular reasons) and secondary (death from any cause, death from cardiovascular reasons, unplanned hospitalization) end points were demonstrated
MORE-CARE trial	865 patients	Patients with implanted CRTDs were enrolled and randomized into remote and standard follow-up arms	1. No significant differences in the composite of death and hospitalization due to cardiovascular and device-related reasons between these two groups were demonstrated 2. A significant 38% reduction in healthcare resources utilization in the remote arm (2-year rates of cardiovascular hospitalizations, cardiovascular emergency department admissions, and cardiovascular in-office follow-ups) as compared with the standard arm was demonstrated

(Continued)

Table 1. (Continued).

Study	Number of patients included	Study protocol	Results
5. Detection of sleep disorders: the potential implementation of remote monitoring			
DREAM study	40 patients	Patients with implanted CIEDs and incorporated Sleep Apnea Monitoring (SAM algorithm) were enrolled. Sleep apnea diagnosis was confirmed by polysomnography as a gold standard diagnostic technique and compared with the respiratory disturbances index evaluated by the SAM algorithm	1. 88.9% sensitivity (95% CI 65.3–98.6%) 2. 88.9% positive predictive value (95% CI 65.3–98.6%) 3. 84.6% specificity (95% CI 54.6–98.1%)
6. Remote monitoring with implanted monitoring-only devices			
COMPASS-HF	274 patients	Patients were randomized into Chronicle device and standard groups	1. Reduction in HF admissions or urgent follow-up visits in Chronicle group by 21% (P = .33) – NS 2. Retrospective analysis has demonstrated a statistically significant 36% reduction in relative risk of the time to first hospitalization in the Chronicle group
REDUCEhf trial	1300 patients (designed to enroll); 400 patients enrolled	Patients with an indication of ICD implantation was enrolled (ICD implantation with an RV pressure monitoring)	1. The trial was prematurely terminated due to technical complications after enrolment 2. No benefit from hemodynamics monitoring has been demonstrated
CHAMPION trial	550 patients	Patients with NYHA Class II were included and randomized into the CardioMEMs and usual monitoring groups	1. Statistically significant reduction in HF hospitalization (regardless of LV ejection fraction) by 28% and 37% in the CardioMEMS group over 6- and 15-months of follow-up, respectively 2. Rates of non-HF-related hospitalizations were similar in both groups 3. Patients included in the CardioMEMS group had a significant reduction in the mean pulmonary artery pressure and better quality of life during the 6-month of follow-up based on the Minnesota Living with Heart Failure Questionnaire
HOMEOSTASIS study	40 patients	Patients with NYHA class III-IV HF were enrolled to receive a HeartPOD device to directly measure LA pressure. The follow-up period was divided into the first blinded (3 months), the second titration (3 months) and the third stability periods (19 months)	HeartPOD group had statistically significant: 1. Improved control of LA pressure 2. Improvement in NYHA class 3. More optimal neurohormonal antagonist dosing 4. 59% reduction of clinical events in the titration and stability period as compared with observation period

NS: nonsignificant; HF: heart failure; AF: atrial fibrillation; RV: right ventricle; LA: left atria, CIED: cardiac implantable electronic device; ICD: implantable cardioverter defibrillator; CRTP: cardiac resynchronization therapy; CRTD: cardiac resynchronization therapy with ICD function.

Considering the aforementioned data, the patient management can be changed in response to the detection of an asymptomatic episode of AF. This is of particular importance given the fact that in the light of the recent data, the routine oral anticoagulation use in chronic HF patient has been dropped [3]. Possible delay (i.e. infrequent office visits) may be associated with an increased risk of thromboembolic (TE) complications. The latter can be prevented by remote monitoring with implanted CIEDs. In 20% of 166 included patients (single-center study; 73% pacemakers; 27% ICDs; 16 months of follow-up) had alerts triggered by AF [65]. In 88% of these patients clinical intervention (i.e. drug therapy modification, device reprogramming, electrical cardioversion) was required. More than 3 million transmissions were sent by 11,624 patients with implanted ICDs and CRTDs included in the worldwide Home Monitoring database [66]. Around 60% of these alerts were due to AF episodes. The TRUST trial included 1339 patients with ICDs [67]. AF detection occurred at 5.5 days in the remote monitoring group compared with 40 days in the standard follow-up group. A total of 1997 patients with implanted ICDs were followed for 15 months in the CONNECT trial [68]. The interval between AF episode detection and clinical response was eight times shorter in the remote monitoring group compared with the standard follow-up group (3 vs. 24 days). Despite the presented data, currently, there is limited evidence suggesting that remote monitoring is associated with reduced risk of AF-related complications. Results from the Monte Carlo simulations suggested that daily monitoring could reduce the 2-year stroke risk from 18% to 9% for an absolute reduction from 0.6% to 0.2% per every 2 years, compared to conventional follow-up at intervals of 6–12 months [69]. The COMPAS randomized, multicenter, non-inferiority trial (538 patients randomized to remote monitoring follow-up vs. standard care) examined the safety of long-term remote monitoring of pacemakers [70]. During an 18.3 months follow-up there were 17.3% vs. 19.1% (P < .01 for non-inferiority) patients who experienced at least one major adverse event (all-cause death, hospitalizations for device-related or cardiovascular events) in the remote monitoring group and standard care group, respectively. Hospitalizations for atrial arrhythmias (6 vs. 18) and strokes (2 vs. 8) were fewer (P < .05), and the number of interim ambulatory visits was 56% lower (P < .001) in the remote monitoring than the standard care group. However, no improvement in the outcome of stroke or all-cause mortality was demonstrated in the IMPACT study [71].

Overall, around one-third of patients with implanted CIEDs experienced asymptomatic episodes of AF. Patients from this cohort have an increased risk of TE complications. Remote monitoring is a unique technique for the early detection of asymptomatic episodes of AF and early management. The potential benefits have to be proven by the further studies.

Heart rate variability (HRV) as a measure of an autonomic function has been of interest. Aronsov et al. have demonstrated that a decrease in HRV is associated with a worsening of HF and an increased risk of death [72]. Meanwhile, Adamson et al. have demonstrated in 288 patients with NYHA class III to IV that an automated algorithm to detect decreases in heart rate variability had 70% sensitivity for predicting detecting hospitalization but was associated with a high false-positive rate [73].

4.4. Detection and management of system-related complications in patients with implanted CIEDs

As mentioned above, remote monitoring may play an important role in the early diagnosis and management of system-related complications in patients with implanted CIEDs [41]. The number of CIED implantations among HF patients has increased exponentially. Expert consensus advises in-clinic checks at 3–6-monthly intervals with increased frequency in response to product advisories [55]. Unfortunately, patients with implanted CIEDs experience a significant number of system-related complications. The majority of which are lead-related complications (due to insulation defect or conductor disruption). The annual failure rate of 10-year-old defibrillation leads is approximately 20% [74]. A significant number of observational studies and randomized clinical trials have demonstrated the beneficial effect of remote monitoring on outpatient management of ICD patients [75–82]. The TRUST trial has shown that remote monitoring is safe and allows earlier detection of events as compared with standard follow-up [83]. Spencker et al. have performed a retrospective cohort analysis of 54 patients with an ICD lead failure [84]. The authors have concluded that in 91% of all lead-related ICD complications, the diagnosis could be established correctly by an alert from the remote monitoring system. A total of 40 recipients of a high-voltage lead, prone to fracture, were remotely followed in the ECOST (Effectiveness and Cost of ICDs Follow-up Schedule with Telecardiology) trial [80]. Over a mean follow-up of 22 ± 4 months after implantation, the failure rate was 7.5%. Remote Monitoring allowed the early and reliable detection of three lead fractures, manifested by the sensing of noise artifact, abrupt rise in pacing impedance, or both, without requiring the intervention of patients in the diagnosis or decision-making process (Table 1).

The results of these studies emphasize the need for continuous monitoring of implanted defibrillation systems. Remote monitoring of devices offers the possibility of continuous observation, early detection of lead failures and fast decision-making.

4.5. Detection of hemodynamic deterioration in heart failure patients

Many commercially available CIEDs enable the measurement of intrathoracic impedance that may predict HF decompensation since the majority of HF patients demonstrate volume overload in the pulmonary circulation caused by an elevated left ventricular (LV) filling pressure. Yu et al. have demonstrated in 33 patients with NYHA class III and IV HF that intrathoracic impedance is inversely correlated with pulmonary capillary wedge pressure and fluid balance and typically decreased before patient become symptomatic [85]. Abraham et al. demonstrated the superiority of intrathoracic impedance monitoring compared with daily weight monitoring in patients with mild to moderate chronic systolic HF in patients with implanted devices (ICD, CRTD) for the first time in 2011

[86]. A reasonable balance between sensitivity and specificity of intrathoracic impedance measurement was demonstrated by Ypenburg et al. in patients with implanted InSync Sentry CRTDs [87]. In contrast to the results of earlier studies, Conraads et al. have demonstrated in the SENSE-HF trial (501 patients) that an intracardiac impedance-derived fluid index had low sensitivity and positive predictive value in the early period (6 months) after implantation of a device in chronic HF patients. Meanwhile sensitivity improved within the first 6 months after implantation [88]. Similar results have been demonstrated by van Veldhuisen et al. in the DOT-HF (Diagnostic Outcome Trial in Heart Failure) study that included 335 patients with an implanted CIED [89]. Patients were randomized to have information available to physicians and patients as an audible alert when a preset threshold was crossed (access arm) or not (control arm). Treatment guided by routine monitoring of intrathoracic impedance was not associated with a better outcome but was associated with an increased likelihood of HF hospitalization. The impedance monitoring has been scrutinized in the PARTNERS-HF trial (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure) [90]. Patients with implanted CRT-Ds (Medtronic devices equipped with intrathoracic impedance monitoring called Opti-Vol) were enrolled. It was demonstrated that reduced impedance (or increased fluid index) was the most sensitive parameter to predict HF hospitalizations. Cowie et al. published the study for the development and validation of a dynamic heart failure score based on the following parameter monitored by implanted ICDs or CRTs: intrathoracic impedance, heart rate variability, arrhythmia burden and patient activity [91]. The data set consisted of 921 patients with an average follow-up duration of 10.6 ± 5.8 months. They demonstrated that patients with a high-risk score have a 10 times more chance of hospitalization compared to patients with a low score. It is not clear whether clinical actions initiated by the stratified risk will have a positive impact on the course of HF or not. The IN-TIME prospective, randomized, controlled, multicenter trial analyzed 664 patients with NYHA class II and III with implanted ICDs and CRTDs [92]. Patients were randomized to either standard care or to remote monitoring. In the telemonitoring group, in response to telemonitoring observations, the investigators initiated a standardized telephone interview to establish whether the patient's overall condition or symptoms had worsened or not, whether there was a sudden increase in body weight (>2 kg within the preceding 3 days) or if a visit to the family doctor was scheduled. There were 63 patients (18.9%) with a declining composite clinical score in the telemonitoring group compared with 90 patients (27.2%) in the control group (P = .013). Mortality among patients involved in the telemonitoring group was lower compared to the control group (n = 10 vs. 27). There were no significant differences in hospitalization between these groups. Results of the world's largest remote monitoring study REM-HF trial (Remote Management of Heart Failure Using Implantable Electronic Devices) was recently presented at the ESC Congress 2016 [93]. A total of 1650 HF patients with implanted CIEDs (ICD, CRTP, CRTD) featuring remote monitoring were enrolled in the study and were randomized to receive either standard care (824 patients) or remote monitoring (826 patients). The median follow-up was 2.8 years. Medical treatment and management of patients (possible medication and lifestyle changes, need for additional clinic visits, recommendations to visit their general practitioner or the emergency room) who received a remote monitoring was based on the data healthcare professionals received on a weekly basis from the device. Patients in standard care group received conventional care from the heart failure service and remote monitoring of the device (once per 3–6 months). There were no significant differences neither in the primary end point (death from any cause or unplanned hospitalization for cardiovascular causes) nor in the secondary end point (death from any cause, death from cardiovascular diseases, unplanned hospitalization). Hence, the REM-HF trial demonstrated that remote monitoring was not associated with reduced mortality or fewer cardiovascular hospitalizations compared to standard care (Table 1).

Recently, the MORE-CARE (Monitoring Resynchronization Devices and Cardiac patients) prospective, multicenter, randomized controlled trial has been published, which evaluates the clinical efficacy and safety of remote monitoring compared with standard follow-up strategies in HF patients implanted with biventricular ICD [94]. A total of 865 patients were included and randomized into a remote arm (n = 437; remote checks alternating with in-office follow-ups) and a standard arm (n = 428; in-office follow-ups). The primary end point of the study was a composite of death and hospitalization due to cardiovascular and device-related causes. There were no significant differences in the primary end point between these two groups. There was a significant 38% reduction in healthcare resources utilization in the remote arm (i.e. 2-year rates of cardiovascular hospitalizations, cardiovascular emergency department admissions, cardiovascular in-office follow-ups) as compared with the standard arm. This is mainly explained by a reduction of in-office visits, despite a slightly higher rate of unscheduled visits in the remote arm (IRR: 2.80, 95% CI 2.16–3.63, P < .001).

Hindriks et al. performed a meta-analysis of the TRUST, ECOST and IN-TIME trials [95]. Pooled data-analysis of 2405 patients, demonstrated that remote monitoring with Biotronik Home Monitoring was associated with a 38% reduction in all-cause mortality as compared with conventional office follow-ups alone after 1 year of follow-up. The combined risk of all-cause mortality or hospitalization for HF decompensation was 36% lower in the remote monitoring group.

The presented results demonstrated that remote monitoring with implanted therapeutic devices may play an important role in an early diagnosis of HF decompensation. Meanwhile, significant differences exist between devices from different manufacturers (with respect to system technologies and feasibilities, data acquisition capabilities, process and workflow options), which can have an impact on their effectiveness to improve outcomes.

4.6. Detection of sleep disorders: the potential implementation of remote monitoring

Patients with HF often complain of sleep disorders such as sleep fragmentation or nonrestorative sleep, difficulties in

initiating sleep, or waking up too early in the morning [96]. Insomnia is more common among HF patients compared to the general population (33% vs. 10–15%), which can be associated with mood disorders and psychological stress [97]. HF patients can have secondary insomnia due to HF itself or from the adverse effects of prescribed medication (angiotensin-receptor blockers, loop diuretics, β-blockers, and statins) [98]. The prevalence of sleep-related breathing disorders is high among HF patients, which is reported to have an important added prognostic value in HF [97]. Sleep-disordered breathing is presented in two major forms: obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA results from the complete collapse of the pharyngeal soft tissues, mainly soft palate and tongue base, CSA arises from fluctuations in the central respiratory drive [97]. A mixed sleep apnea is a third form of sleep-disordered breathing and characterized by an initial central apnea event followed by an obstructive component. Nearly 50% of HF patients have central or obstructive apneas and hypopneas that decrease the positive effects of physiological sleep on the cardiovascular system [99,100]. Sleep-disordered breathing is associated with a high sympathetic activation which can negatively affect the prognosis of HF patients [101–103]. Continuous positive airway pressure (CPAP) is a treatment modality for patients with OSA. CPAP therapy in patients with HF and OSA prevents recurrent hypoxia, reduces nocturnal blood pressure and heart rate, and increases arterial baroreflex sensitivity [104,105]. CPAP treatment was associated with a significant increase in a mean LV ejection fraction (LVEF) and reduction in dyspnea in the study of Malone et al. published in 1991 [106]. It was the first study which demonstrated the positive influence of CPAP therapy in HF patients. Kauta et al. have demonstrated that CPAP therapy was associated with a reduced hospital readmission rate and emergency department visits of HF patients over a 30-day observation period [107]. Randomized trials have also demonstrated the association between CPAP therapy and LVEF improvement, reductions in blood pressure, heart rate and sympathetic nerve activity [108,109]. A meta-analysis of 10 randomized clinical trials performed by Sun et al. has demonstrated that CPAP therapy may significantly improve LVEF in HF patients [110]. However, there are no randomized controlled trials demonstrating the effect of CPAP therapy on mortality among HF patients with OSA. In addition, the scientific statement on sleep apnea and cardiovascular disease from the AHA/ACC Foundation considers CPAP treatment in patients with HF as being investigational because this treatment option is not supported by randomized trial data [111].

CIEDs with incorporated Sleep Apnea Monitoring (SAM) system have been recently developed. SAM has been designed to detect, count and report breathing disorders during the night. A total of 40 patients with indications for pacemaker implantation were involved in the DREAM European study [112]. Sleep apnea diagnosis was confirmed by polysomnography as a gold standard diagnostic technique and compared with the respiratory disturbances index evaluated by the SAM algorithm complied from the device during the same diagnosis night (Table 1). The study has demonstrated that an advanced algorithm could be used to identify sleep apnea in patients with pacemakers outside the clinic or at home.

The results of these studies emphasize the need for the further research in the sphere of CPAP therapy in HF patients with OSA. CIEDs with incorporated sleep apnea detection facilities and remote monitoring may play a crucial role in the early detection of OSA in HF patients and improvement of hemodynamics with CPAP therapy. Whether the latter will improve the survival among HF patients has to be clarified by randomized trials.

4.7. Remote monitoring with implanted monitoring-only devices

Implanted monitoring-only devices are hemodynamic monitors measuring intracardiac or intravascular pressures. These monitors presented by right ventricular, pulmonary artery and left atrial pressure monitors. The basic pathophysiology of HF (i.e. cardiac filling pressures determine the clinical symptoms and course of HF) lies behind the idea of using such monitors in clinical practice [113].

Medtronic Inc has developed the Chronicle, implantable hemodynamic monitor, which is a long-term implanted device consisting of a subcutaneously implanted generator and a unipolar transvenous pacemaker lead, carrying a pressure sensor, positioned in the RV outflow tract that records RVSP, RVDP and estimation of PAP. A total of 274 patients with NYHA class III-IV HF on optimal medical therapy were included in the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) prospective, multicenter, randomized, single-blinded, parallel-controlled trial and randomized into the Chronicle device group (n = 134) and standard group (n = 140) [114]. Primary end points of the study were freedom from system-related complications, freedom from pressure sensor failure and reduction in the rate of HF-related hospitalizations or emergency visits (Table 1). The complication-free rate was 91.5% at 6-month of follow-up. A statistically nonsignificant reduction in HF admissions or urgent follow-up visits by 21% (P = .33) in the Chronicle group has been demonstrated. A retrospective analysis has shown a statistically significant 36% reduction in relative risk of the time to first hospitalization in the Chronicle group. A new trial, REDUCEhf was designed to enroll 850 patients (then increased to 1300) with an indication for ICD (NYHA class II-III, impaired LV ejection fraction) therapy, to test whether use of RV pressure-guided patient management would reduce HF-related adverse events or not [115]. The trial was prematurely terminated due to technical complications after the enrolment of 400 patients. No benefit from hemodynamic monitoring was been demonstrated.

St Jude Medical (acquired by Abbott) has developed a catheter-delivered pressure sensor (15-mm long, 3-mm wide) that is permanently implanted in the pulmonary artery via right heart catheterization, called Cardio-MEMS. The device consists of a wireless 3D coil and a pressure-sensitive capacitor covered with silicone. A total of 550 patients with NYHA class II HF were included in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes

in NYHA Class II Heart Failure Patients) prospective, multicenter, single-blind clinical trial and randomized either to the CardioMEMS (n = 270 patients) or standard monitoring (n = 280 patients) groups [116]. The study has demonstrated a statistically significant reduction in HF hospitalization (regardless of LV ejection fraction) by 28% and 37% in the CardioMEMS group over a 6- and 15-month follow-up, respectively. Rates of non-HF-related hospitalizations were similar in both groups. Patients included in the CardioMEMS group had a significant reduction in the mean pulmonary artery pressure and better quality of life during the 6-month follow-up based on the Minnesota Living with Heart Failure Questionnaire.

St Jude Medical (acquired by Abbott) has also developed a HeartPOD device to directly measure LA pressure, core temperature and intracardiac electrograms, by a sensor lead placed intra-atrially through a transseptal puncture, which is then linked to a sub-pectoral antenna. A total of 40 patients with NYHA class III-IV HF were included in the HOMEOSTASIS (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients) prospective, observational, first-in-human study. The follow-up period was divided into three parts: the first 3 months (patients and clinicians were blinded to LA pressure readings), the second 3 months was a titration period (therapy adjustment to find an optimal LA pressure), and stability period (therapy adjustment to maintain an optimal LA pressure) [117]. The total follow-up period of the study was 25 months. Patients included in the HeartPOD group had statistically significant improved control of LA pressure, improvement in NYHA class, enhanced neurohormonal antagonist dosing and a 59% reduction of clinical events in the titration and stability periods as compared with the observation period.

Overall, theoretically, implantable hemodynamic monitoring devices may play an important role in the early detection of HF decompensation. However, there is no clear evidence in regard to the sensitivity of such devices in the early detection of HF decompensation. The latter has to be demonstrated in large randomized trials.

5. Expert commentary

Clinical management to prevent acute decompensation and/or readmission in ambulatory HF patients remains challenging. Overall, chronic HF is the 'oncological' cardiac disease with grave prognosis, unless appropriate optimal medical and device based therapies are instituted. Once the unstable, decompensation periods begin, the progression of HF is usually irreversible. Consequently, efforts should be made to decrease HF incidence and prevalence and improve survival among HF patients by the early detection of disease deterioration and timely changes in the treatment of affected patients. A number of new techniques for the diagnosis and treatment of HF have been developed and introduced into clinical practice. Remote monitoring is a spectacular tool in the arsenal of cardiologists that has been designed to facilitate an early detection of adverse events and to minimize regular follow-up visits of HF patients. Nowadays, several possible tools are available for the remote monitoring of HF. Structured trans-telephonic support and telemedicine has shown variable clinical results

in prevention of the deterioration of HF. The data on remote monitoring of HF patients with CIEDs are still controversial, due to the presence of significant differences in different manufacturers' devices (system technologies and feasibilities, data acquisition capabilities, process and workflow options). Meanwhile, remote monitoring is feasible and may facilitate early detection of system-related complications. However, as with every new technology, there are areas of uncertainty. Because there is not one universal approach, each device needs to be assessed on its individual merit in individual patients. The biggest challenge is to provide a platform which will allow the rapid and simple interpretation of the remote monitoring data that produces a targeted and effective response. The diagnostic, therapeutic and preventive potential of remote monitoring remains undefined in terms of cost/risk/benefit ratio. This is currently one of the limitations of such devices.

Overall, early intervention in response to remote monitoring registration may help to prevent the decompensation of HF. Meantime, remote monitoring provides a large amount of information. Further research by way of randomized clinical trials has to identify the parameters which play the most important role in the management of HF patients.

6. Five-year view

Recently published trials on remote monitoring call to develop the next generation of tools with better algorithms to help triage alerts and simplify interpretation of data, directed to impact clinical outcomes. The next generation of remote monitoring technology would be developed to identify what is important in all the data streams and also enable nurses, technologists and physicians to know what action to take at the right time. The whole system of remote monitoring can be more visionary and, which is very important, more user friendly (e.g. simple and understandable programming of devices and recorded information retrieval). Further improvement in the technical aspects will allow the reduction in the rate of false alarms. Wireless charging of implanted CIEDs may become an alternative to frequent device changes. Most probably the future generation of CIEDs will incorporate pressure sensors which will allow a continuous monitoring of intracardiac and intravascular pressures. Continuous blood pressure monitoring and better LV lead performance, direct coupling to medication change, self-assessment based medication changes, possible involvement of mobile devices with specifically developed applications and artificial intelligence will improve management and outcome of HF patients.

Key issues

- Chronic HF is a cardiovascular disorder that affected approximately 1–2% of adult population worldwide.
- Incidence and mortality of HF are decreasing in developed countries.
- The course of HF is characterized by periods of stability and instability. Deterioration of HF is associated with frequent

and prolonged hospitalizations and it worsens the prognosis for the disease and increases cardiovascular mortality among affected patients.

- Remote monitoring has been designed to facilitate an early detection of adverse events and to minimize regular follow-up visits for heart failure patients.
- The data on remote monitoring of HF patients with CIEDs are still controversial, due to the presence of significant differences in different manufacturers devices (system technologies and feasibilities, data acquisition capabilities, process and workflow options).
- As with every new technology, there are areas of uncertainty. The diagnostic, therapeutic and preventive potential of remote monitoring is still undefined in terms of cost/risk/benefit ration.
- A special platform has to be invented to make daily use of all the recorded information fast and easy.
- The whole system of remote monitoring can be more visionary and, which is very important, more user friendly. Further improvement in the technical aspects will allow the reduction in the rate of false alarms.

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