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Implantable devices to monitor patients with heart failure

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Abstract

Reducing heart failure hospitalizations represents a major challenge for modern clinicians. Early detection of congestion plays a key role in disease management strategy. Apart from traditional methods (patient reporting symptoms, body weight monitoring), novel home-care strategies allow guided adjustments in medical therapy through telemonitoring embedded in cardiac electronic implantable devices or through stand-alone diagnostic devices for hemodynamic monitoring. Wireless pulmonary artery pressure monitoring seems to reduce re-admission risk and is currently approved for this purpose in patients with heart failure. Multiparameter monitoring is also appealing and could be a valuable tool in managing these patients. However, invasive techniques face several safety concerns and cost-effectiveness issues. Therefore, quest for future research and emerging technologies is necessary.

Keywords Telemonitoring · Heart failure · Implantable hemodynamic monitoring devices · Cardiac resynchronization therapy · Implantable cardioverter defibrillator · Review

Introduction

Heart failure (HF) still carries a tremendous clinical and financial burden, despite considerable advances in the perception of its pathophysiology and a plethora of therapeutic options [1]. Over the years, joined forces by major cardiovascular and electrophysiological societies have provided thorough evidence-based therapies, including optimal medication with neurohormonal antagonists and dedicated devices such as implantable converter-defibrillators (ICDs) and cardiac resynchronization therapy devices (CRTs) [2–5]. Nevertheless, in the United States of America (USA), HF is credited as the primary diagnosis in more than one million patients hospitalized annually, and in Europe, the 24% of patients suffering from HF is re-admitted within 12 weeks after discharge [1, 6]. HF-related costs represent 1–2% of total healthcare expenses, mostly due to recurrent hospitalizations [7]. Transition from stable compensated to acute decompensated HF (ADHF) leads to recurrent hospitalizations and is a milestone event that marks disease progression. More importantly, re-admissions due to ADHF are related to increased rates of morbidity and mortality, regardless of age and renal function [8]. Thus, the need for early prediction and intervention in order to reduce ADHF events is critical.

Identifying the failing myocardium, conventionally by physical examination, HF signs, symptoms, and changes in body weight, is often ineffective in preventing HF hospitalization, because these events manifest late during HF exacerbation and are relatively unreliable and also requires in-clinic visits [9]. Body weight monitoring in predicting HF decompensation has a sensitivity of 10–20% and when symptoms, such as shortness of breath, orthopnea, or leg edema, are present, the attempt to prevent hospitalization is usually vain [10]. Autonomic adaptation and decrease in intrathoracic impedance due to increased lung fluids precede symptoms of clinical congestion [11]. The earliest events and most accurate signs predicting HF deterioration are changes in intracardiac and pulmonary artery pressure (PAP), which can occur several days or even weeks before clinical congestion is present (Fig. 1) [12]. Application of a pro-active strategy, using pressure-guided therapy and maintaining a patient in a "safe zone", within an ideal range of values, seems preferable to a merely crisis management, triggered by alert events [13]. The apparent need for monitoring HF patients at home led to an

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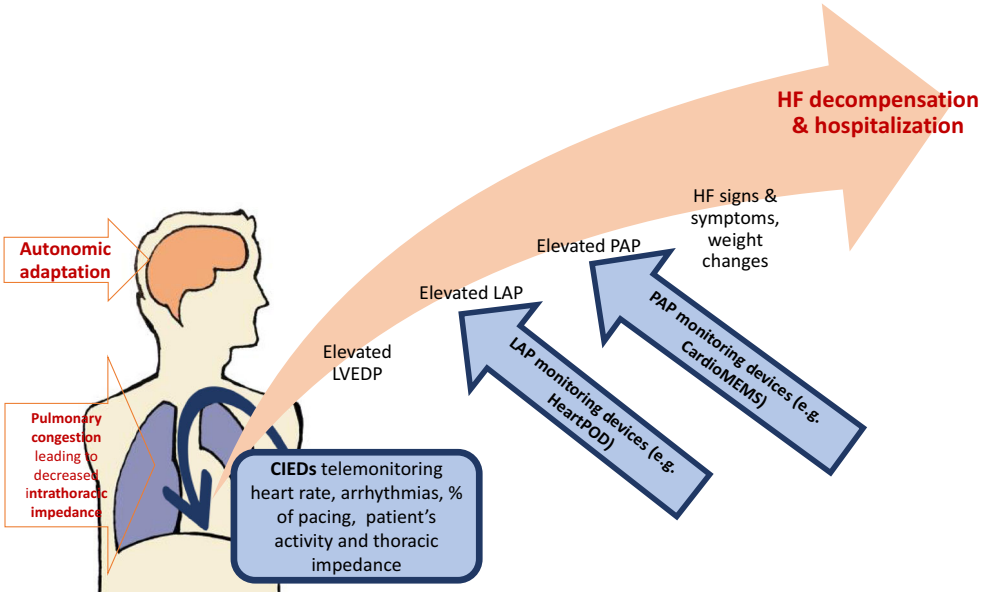

Fig. 1 Implantable HF monitoring devices. Elevation in intra-cardiac pressures and PAP occur several days or weeks before clinical congestion, leading to HF decompensation and hospitalization. HF, heart failure; LVEDP, left ventricular end diastolic pressure; LAP, left atrial pressure; PAP, pulmonary artery pressure; CIEDs, cardiac implantable electronic devices

ongoing pursuit using various technological systems. Data of clinical interest such as symptoms, physical signs (blood pressure, heart rate, and body weight), oxygen saturation, ECG strips, arrhythmic events, device diagnostics, thoracic impedance, and hemodynamic pressures can be collected, depending on the regime applied. Historically, various strategies of monitoring outpatients have been studied and can be divided into two categories: structured telephone support (STS) and telemonitoring (TM). STS consists of fixed telephone communications, once or twice a month, performed mostly by trained nurses, assessing related symptoms, evolving education even physiological data, e.g., body weight. Several studies were conducted and their results have been reviewed elsewhere [14–19]. Recent breakthroughs in medical microelectronics render long-term ambulatory monitoring in HF patients feasible, by transmitting circulative patient data digitally to a secure web location, aka telemonitoring. Monitors embedded to cardiac implantable electronic devices (CIEDs) such as ICDs and CRTs or even stand-alone diagnostic implantable monitors have been developed, promising to reduce ADHF events and improve HF patient outcomes (Fig. 1). So far, clinical experience in implantable HF monitors is limited; in addition, experts agree that conduction and evaluation of clinical trials regarding these devices can be cumbersome [20]. The goal of this review is to focus on implantable HF monitors, including dedicated stand-alone hemodynamic monitoring devices or piggybacked to CIEDs with added features.

Implantable hemodynamic monitoring devices

Elevated left ventricular end-diastolic pressure (LVEDP) leading to elevated left atrial pressure (LAP) and pulmonary congestion marks the progression from stable chronic HF to ADHF and hospitalization (Fig. 1) [12]. Remote monitoring systems for "pressure guided therapy" have been developed over the past years in order to apply tailor-made therapy for HF patients and prevent such re-hospitalizations (Fig. 1). So far, one implantable hemodynamic monitor (IHM) has been approved by the Food & Drug Administration (FDA) in the USA, notably the CardioMEMS HF system (Abbot, Sylmar, California) for PAP monitoring. It has also been added to the European Society of Cardiology (ESC) guidelines as a directed therapy management and monitoring tool for HF patients [2].

Right ventricular pressure monitoring systems

The pioneer study featuring intracardiac pressure findings in HF was performed using implanted micromanometers in the right ventricle (RV) and pulmonary artery (PA), by estimating the diastolic PAP during PA valve opening, in ten patients in comparison to conventional PA catheter pressure [21]. Embracing this concept, gave birth to the Chronicle device (Medtronic Inc., Minneapolis, Minnesota), which consisted of a pulse generator and a pacemaker lead implanted in the RV outflow tract, very similar to a common pacemaker. By measuring RV systolic and diastolic pressures, heart rate and pressure derivatives in 32 patients with the Chronicle device, a 25% rise in RV systolic pressure in 36 volume-overload events was noticed and data monitoring lead to a 57% decrease ($p < 0.01$) in hospitalization rate [22]. In the first randomized controlled trial, the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure), the Chronicle IHM was implanted in 274 New York Heart Association (NYHA) III and ambulatory IV HF patients; 70% of them had a left ventricular

ejection fraction (LVEF) > 50%. Randomization to the Chronicle treatment algorithm group with access to hemodynamic data versus usual care without physician access to data, showed a non-significant 21% decrease in HF decompensation events [23, 24]. The primary endpoint of the trial was not reached, so FDA voted against the approval of the device. Despite the initially discouraging results and the fact that a large device had no direct therapeutic action, the COMPASS-HF and retrospective meta-analysis showed that diastolic PAP gradual elevation could predict HF events before conventional signs and symptoms and physician access to PAP management was feasible [25, 26]. Thus, the pursuit for pressure-guided therapy remained challenging, especially if embedded in CIEDs.

Pulmonary artery pressure monitoring systems

As mentioned above, the CardioMEMS HF system for PAP monitoring is the first IHM approved for managing HF patients. It consists of a leadless PAP sensor implanted into the distal PA and an external antenna placed against the patient or merged in pillow (Table 1). Implantation of the sensor is performed using dedicated delivery equipment, during right heart catheterization, with venous (usually transfemoral) access. Resonant frequency findings in the sensor are transmitted electromagnetically to the antenna, converted in PA waveforms and then wirelessly sent to a secure web location, where physicians gain access. Power to the sensor is provided by the external antenna, so there is no battery and no need for replacement. The duration of the procedure is approximately 20 min and interrogation of the system takes about 20 s (Table 1) [27].

After the pilot study for safety and accuracy of the system, 550 NYHA III HF patients, regardless of LVEF, were enrolled in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) Trial [28, 29]. After system implantation, patients were randomized to a treatment group ($n = 270$), in which clinicians had daily access to the pressure findings or to a control group ($n = 280$) in which telemonitoring was hampered. Even though patients were blind to which group they had been randomized, physicians received telemonitoring for the treatment group exclusively and therefore it was not blind to allocation. Counter to the COMPASS-HF trial, in the CHAMPION-specific pressure targets and suitable treatment algorithms were applied and dictated by protocol to ensure reasonable testing of the trial's supposition. The primary endpoint was the rate of heart failure hospitalization due to HF decompensation, during a period of 6 months, but all patients were sustained in the single-blind study allocation until the 6-month follow-up of the last patient [29]. The CHAMPION trial showed a significant reduction of its primary endpoint, from 0.44 in the control group to 0.32 in the treatment group (relative risk reduction: 28%; $p < 0.0002$)

Table 1 System and procedural characteristics. PAP, pulmonary artery pressure; LAP, left atrium pressure; Fr, French gauge; PA, pulmonary artery; LA, left atrium; IU, international units; IV, intravenous; ICE, intracardiac echocardiography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

	PAP monitor	LAP monitor
Device name	CardioMEMS™	HeartPOD®
Access	Venous, usually transfemoral	Venous (femoral and subclavian), transeptal puncture is required
Delivery system	12 Fr introducer sheath, dilators, 110 cm PA catheter, 0.018″ × 260–300 cm guidewire with angled or straight tip	Brockenbrough needle via an 8 Fr sheath, 11 Fr delivery sheath in the LA. 5000 IU of heparin IV are required during the procedure
Imaging	Fluoroscopy, PA angiography	Fluoroscopy, and TEE, TTE, or ICE
Deployment description	Release of preloaded sensor from over-the-wire delivery system to the distal PA	Sensor anchors are fastened to the inter-atrial septum
Related implantable components	None	Coil antenna and lead
Procedure duration	20 min	About 1 h
Interrogation method	Sensor-released energy responding to radiofrequency pulse is detected transcutaneously using the patient electronics unit	The signal of the implanted sensor lead-antenna coil signal is detected transcutaneously using the handheld patient advisory module
Antithrombotic therapy after the procedure	Aspirin and clopidogrel for the first month, afterwards aspirin indefinitely. If chronic anticoagulation is needed, vitamin K antagonists can be used instead of aspirin after the first month	Aspirin and vitamin K antagonist for the first month, afterwards aspirin indefinitely
System longevity	Everlasting	Everlasting

[30]. During the entire single-blinded follow-up period, with a median time of more than 17 months, there was a reduction of 37% in the relative risk of HF hospitalizations. In addition, the treatment group demonstrated a significant reduction in PAP, a significant increase in the number of days alive and out of the hospital for heart failure, a significant reduction in the proportion of patients hospitalized for heart failure, and a significant improvement in quality of life. Device or system-related complications and pressure-sensor failure rates were only 1.4 and 0%, respectively [30]. Interestingly enough, a considerable amount of HF patients ($n = 119$) with mid-range and preserved EF (LVEF ≥ 40%, average LVEF = 50.6%) participating in the trial, also benefited from PAP-guided therapy [31].

The CardioMEMS system gained FDA approval in May 2014 for use in patients NYHA III with at least one hospitalization due to HF in the past 12 months and is added to the latest ESC guidelines as a directed therapy management and monitoring tool for HF patients [2]. Post-approval studies of CardioMEMS in the "real world" are eagerly anticipated; so far, the incoming messages are more than positive. In a recently published study, Heywood et al. have noticed that the first 2000 patients with CardioMEMS had higher PA pressures at baseline and experienced greater reduction in PA pressure over time compared with the historic CHAMPION clinical trial [32]. Patients and physicians developed excellent compliance to the IHM system, the first were committed to receive their prescribed medication and the latter via telemonitoring could adjust medication and doses to lower PAP [32]. Desai et al. have also studied the "real world" use of CardioMEMS and have seen that PAP telemonitoring leads to fewer hospitalizations due to HF and reduces HF comprehensive costs, supporting its "real-world" effectiveness [33]. An analysis published after the first 5500 CardioMEMS devices in the USA, has shown concordance in safety between real-world use during the first 3 years and the CHAMPION trial, where the overall rate of adverse events was 2.6% [34]. A learning curve is required to avoid the most serious adverse events (mainly PA injury and hemoptysis), which is common in every novel interventional approach [34].

With the financial burden of HF hospitalization still at large, reduction of HF hospitalization using IHMs could relieve the health system, provided that the initial investment costs are carefully weighed and do not exceed potential standard care long-term costs. An economic analysis based on the CHAMPION trial has studied the cost-effectiveness of the CardioMEMS HF system, in comparison to the standard of care treatment for HF [35]. With an incremental cost-effectiveness ratio of $44,832 per quality-adjusted life year, the CardioMEMS HF System was found to be in the high-to-intermediate value of what is considered cost-effective, according to the American College of Cardiology/American Heart Association [35, 36].

Besides the CardioMEMS HF system, two other PAP monitoring systems are currently in working progress, one from Medtronic, Inc. (Minneapolis, Minnesota) and another from Endotronix, Inc. (Woodridge, Illinois) [25]. The one from Medtronic Inc. consists of a small sensor with a battery in its capsule communicating to a Reveal LINQ implantable cardiac recorder. It can monitor PAP, heart rate, arrhythmias, and other patient data trends. The PAP monitoring system from Endotronix is very similar to the CardioMEMS, but with a different user interface [25].

Left atrial pressure monitoring systems

Even though PAP is considered to be an acceptable surrogate for filling pressures, LVEDP remains the gold standard for preclinical congestion estimation. Thus, LAP would be a better choice for interpretation as it correlates well with LVEDP, ideally when measured at the "z point," the foot of the atrial c wave [37–39]. While more cumbersome and invasive to implant, an IHM for direct LAP measurement has been developed, the HeartPOD (Abbott, formerly St. Jude Medical/Savacor, Inc.) [40]. The HeartPOD system includes a sensor placed in the LA, coupled to a subcutaneous antenna coil, a patient advisory module and telemonitoring to a secure web location. After femoral venous access and transeptal crossing of the interatrial septum, the tip of the sensor system is delivered to LA, measuring LAP, temperature, and an intracardiac electrogram. The patient's advisory module interrogates and gives power to the implant (Table 1) [40]. In the prospective, observational, first-in-human HOMEOSTASIS trial, the HeartPOD system was implanted in 40 moderately or severely symptomatic HF patients with previous hospitalization(s) [41]. Patients were advised to perform measurements twice daily placing the advisory module over the subcutaneous antenna. In the first 3 months, patients and physicians were blind to measurements and treatment was performed upon clinical signs and symptoms. After the blind period of 3 months, LAP findings were displayed directly on the advisory module to patients, providing information for diuretic dose adjustment. At the end, HF hospitalizations during the titration period were reduced by 59% ($p = 0.04$) compared to the blind period [41].

The LAPTOP-HF (Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy Study) was a prospective, multicenter, randomized, controlled clinical trial, in which the safety and clinical effectiveness of LAP-guided therapy, measured twice daily, in ambulatory patients with advanced HF would be compared with a control group receiving optimal medical therapy [42]. Patients enrolled in the LAPTOP-HF trial were NYHA III meeting at least one of the following criteria: (i) hospitalization for heart failure during the previous 12 months or (ii) an elevated B-type natriuretic peptide level, regardless of ejection fraction. Randomization to the treatment or control group was performed via a 1:1 ratio in three layers,

LVEF > 35%, LVEF ≤ 35%, and the presence of a de novo CRT indication [42]. However, recruitment in this trial ended early, due to a transgression in implant-related complications. Still, preliminary results presented during a Late Breaking Clinical Trials Session at the 2016 Heart Failure Society of America meeting have shown that the overall trial result was negative. There was no reduction in the combined endpoint of HF re-admissions and complications of heart HF therapy [43]. On the other hand, when these preliminary results were analyzed using the CHAMPION trial formula and endpoint, the LAPTOP-HF demonstrated its potential, as its results were similar to those of CHAMPION [25].

Despite the initial discouraging effort of the HeartPOD system, LAP monitoring systems are still in development, namely the V-LAP system (Vectorious Medical Technologies, Tel Aviv, Israel) and another surgically implanted from Titan, ISS Inc. (Ypsilanti, Michigan) [25, 44].

ICD/CRT device diagnostic monitoring for HF patients

Telemonitoring embedded in CIEDs has obvious advantages and seems appealing; besides therapeutic features (pacing, anti-tachycardia pacing, shocks, and CRT), diagnostic features such as arrhythmia event logbook, percentage of atrial and ventricular pacing, mean heart rate, and patient's physical activity can be accessed remotely.

As mentioned above, increased pulmonary congestion decreases thoracic impedance, predicting HF aggregation before weight change and clinical signs and symptoms [11]. In the SENSE-HF (sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations) trial, intrathoracic impedance measurements were performed in 501 HF patients with a newly implanted ICD, with or without CRT, using the OptiVol® (Medtronic, Inc.) algorithm [45]. The OptiVol® function received FDA approval in 2004. In this trial, the sensitivity to predict HF events was at best 42% with a positive predictive valve of 38% and it also revealed many practical uncertainties such as unreliability of impedance testing early after implant [45]. OptiVol® was also studied in the Diagnostic Outcome Trial in Heart Failure (DOT-HF), but the trial was terminated early because of under-recruitment. Still, post-hoc analysis has shown that mortality and re-admissions for HF would not have a significant reduction, even if recruitment was ideal [46, 47].

In the Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure (REDUCE-HF) trial, 400 NYHA II-III patients were enrolled with an ICD indication and a previous HF hospitalization [48]. The implanted ICD had hemodynamic monitoring abilities and patients were randomly assigned to a treatment group and to a control group with no hemodynamic information. Due to early enrolment termination, the trial's primary clinical effectiveness hypothesis could not be studied sufficiently because of early recruitment closure. Still, the rate of HF equivalents was not different between the treatment and control groups [48].

The Optilink-HF (Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink) trial, used an OptiVol/CareLink® system (Medtronic, Inc.) to provide physicians with wireless alerts of threshold deviations for worsening cardiac status [49]. Among patients with advanced HF that received ICD with telemonitoring capacities, fluid status telemedicine alerts did not significantly improve outcomes [50].

Based on an HF aggregation diagnostic algorithm, including data such as long periods of atrial fibrillation (AF), rapid ventricular response rate during AF, high night heart rate, low physical activity, low percentages of bi-ventricular pacing, low heart rate variability, high fluid index and ICD shocks, the PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) trial was conducted [51]. This multicenter trial included 694 patients that received CRT-D and based on the above algorithm, monthly review identified the ones at high risk for HF hospitalization. Patients assembling positive device diagnostics had a hazard ratio of 5.5 (95% CI 3.4–8.8; $P < 0.0001$) of HF hospitalization within 1 month [51].

In the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study, 200 patients with a Medtronic wireless ICD/CRT-D with the CareLink network were randomized into two groups [52]. The first group had telemonitoring features enabled, while the second (control group) had telemonitoring blocked. In the control group, audible alerts were turned on with no transmission of data; in the treatment group, all alerts were transmitted with no audible alerts. The primary endpoint of the trial was emergency department or out-of-schedule in-office visits, and then secondary endpoint included visits related to episodes of HF worsening arrhythmia-related visits or ICD-related events. In the remote monitoring group, health-care use was reduced as well as clinical visits (35% less, $p = 0.005$), visits for heart failure, arrhythmia- or ICD-related events (21%; $p = 0.001$), and time from ICD alert to review (24.8 days in the control group vs. 1.4 days in the treatment group, $p = 0.001$). In addition, telemonitoring significantly improved quality of life based upon the Minnesota Living With Heart Failure Questionnaire ($p = 0.026$) [52].

IN-TIME (implant-based multiparameter telemonitoring of patients with heart failure) was a multicenter prospective, randomized, and controlled trial sponsored by BIOTRONIC SE & Co.KG (Berlin, Germany) using sophisticated multiparameter telemonitoring in chronic HF patients [53]. Seven-hundred and sixteen patients with an indication for ICD or CRT-D were enrolled, 664 of them were randomized into two groups, one with telemonitoring features ($n = 333$) and one control group applying only standard care ($n = 331$).

Patients randomized were already receiving optical medical treatment, with a LVEF ≤ 35% (mean LVEF 26%), mostly NYHA III (57%) and NYHA II (43%). Multiparameter monitoring included events of ventricular tachyarrhythmias or shocks, atrial tachyarrhythmias, CRT pacing less than 80% for 48 h, ventricular premature contractions > 110 per hour or an increasing trend over 7 days, decreasing patient activity over 7 days, abnormal IEGM or sensing safety notifications, pacing or impedance safety notification, and finally gap in data transmission for more than 3 days. Follow-up lasted for 1 year; primary outcome of the trial was a composite clinical score (modified Packer score) combining all-cause death, overnight hospital admission for heart failure, change in NYHA functional class, and change in patient global self-assessment, for the intention-to-treat population [54]. At 12 months, significantly fewer patients in the home-monitoring group had reached the primary end point, worsening by modified Packer Score, as well as fewer home-monitoring patients died of any cause over the study period. The IN-TIME study alone had already shown a more than 50% risk reduction for all-cause mortality in heart failure patients specifically [54]. It was the first randomized controlled trial showing a significant benefit of device-embedded multiparameter telemonitoring on the clinical status in HF patients. It has shown that telemonitoring is feasible and should be applied in clinical practice.

In the REM-HF (Remote Management of Heart Failure using Implanted Devices and Formalized Follow-up Procedures) study, conducted at 9 British hospitals, 1650 HF patients (mean age = 70 years old) had CRT-P, CRT-D, or ICD implanted with remote monitoring features [55]. The patients were randomized to receive either standard care (control group) or remote monitoring [55]. Patients in the remote monitoring group had data downloaded automatically from their device weekly and data report was transmitted to their physicians providing instructions about medication and lifestyle, further in-clinic visits, or urgent visits at the emergency room. On the contrary, patients in the control group did not have weekly automatic downloads, just usual remote monitoring of their CIED (typically 3–6 monthly), with additional standard care from their HF service. The primary endpoint of the study was the first event of death from any cause or unplanned hospitalization for cardiovascular reasons. Secondary endpoints of the study included death from any cause, death from cardiovascular reasons, and unplanned hospitalization. After a median follow-up period of 2.8 years, no significant difference was demonstrated between the two groups regarding primary end point events, which occurred in 42.4% of the remote monitoring group and 40.8% of the control group (hazard ratio 1.01; 95% confidence interval [CI] 0.87 to 1.18; $P = 0.87$). In addition, there was no significant difference between the two groups in the secondary end point [56].

Summary

Identifying HF aggravation early, before it leads to hospitalization is critical and remote hemodynamic monitoring can be a valuable tool, improving outcomes in chronic HF patients. Stand-alone diagnostic IHMs or CIEDs piggybacked with telemonitoring features could provide further insight into these patients' physiology, improve compliance and response to pharmacological therapy, while potentially reducing the need and cost for in-clinic visits or invasive hemodynamic procedures. However, clinical use and experience in telemonitoring is still limited; effectiveness and safety regarding data in this patient population must be notably examined. Following the FDA approval of the CardioMEMS HF System, wide experience at major centers sets the pace for more randomized controlled trials. Several questions are yet to be answered and firm conclusions are hard to reach. What kind of patients' population benefits the most, how frequent is this benefit and is this technology cost-effective? Which parameters should be observed and what are the ranges that require action? More importantly are these systems user-friendly, for patients and physicians both, with minimal implantation hazard and complications during their use? These are the million-dollar questions that require future research and need to be unraveled in order to make telemonitoring in HF patient feasible and effective.

Compliance with ethical standards

Conflict of interest Authors Nikolaos Karamichalakis, George Bakosis, Vasiliki Bistola, Ignatios Ikonomidis, and Antonios Sideris declare no conflict of interest. Author John Parissis has received horonaria for lectures from Servier, Novartis, and Roche diagnostics. Author Gerasimos Filippatos is committee member in trials sponsored by Novartis, Medtronic, Bayer, and Servier.

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