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HeartLogic™: real-world data—efficiency, resource consumption, and workflow optimization

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Heart failure (HF) is a major and still growing medical problem and is characterized by episodes of acute decompensation that are associated with a negative prognosis and a significant burden on the patients, doctors, and healthcare resources. Early detection of incipient HF may allow outpatient treatment before patients severely decompensate, thus reducing HF hospitalizations and related costs. The HeartLogic™ algorithm is an automatic, remotely managed system combining data directly related to HF pathophysiology into a single score, the HeartLogic™ index. This index proved to be effective in predicting the risk of incipient HF decompensation, allowing to redistribute resources from low-risk to high-risk patients in a timely and cost-saving manner. The alert-based remote management system seems more efficient than the one based on scheduled remote transmission in terms of caregivers' workload and alert detection timing. The widespread application of the HeartLogic™ algorithm requires the resolution of logistical and financial issues and the adoption of a pre-defined, functional workflow. In this paper, we reviewed general aspects of remote monitoring in HF patients, the functioning and pathophysiological basis of the HeartLogic index, its efficiency in the management of HF patients, and the economic effects and the organizational revolution associated with its use.

Introduction

Heart failure (HF) is a major health, social and economic issue with significant morbidity and mortality worldwide. Incidence and prevalence are expected to increase in the next years due to the higher baseline cardiovascular (CV) risk, lower mortality related to the improved treatment of major cardiac and non-cardiac diseases, and population aging.[1] Nowadays, HF is the first cause of hospital admission among the older population and is the leading cause of death, accounting for 1–3% of the total healthcare financial burden in developed countries. In the US alone, HF-related costs are expected to reach 70 billion dollars by 2030, resulting in an increase of 130% on current costs.[1] The natural history of HF is characterized by periods of clinical stability, interrupted by episodes of acute decompensation, related to increased cardiac filling pressure and/or reduced cardiac output, resulting in systemic and/or pulmonary congestion and hypoperfusion. Acute HF decompensations are associated with disease progression, increased mortality, and hospital admission, which represent the main healthcare cost related to HF syndrome. The early detection of incipient acute HF decompensation is of utmost importance for patients, doctors, and third payers because may allow outpatient treatment before patients severely decompensate, thus reducing HF

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hospitalization and related costs.[2,3] However, early diagnosis of HF decompensation episodes still represents an unmet need in HF management because symptoms and signs of overt HF usually appear late in the pathophysiological chain that leads to HF decompensation.[1] In order to optimize HF management and reduce HF hospitalizations, several telemonitoring (TM) strategies have been implemented in the last decade, with a drastic acceleration in TM adoption during the COVID-19 pandemics to follow-up patients maintaining social distancing imposed by the authorities.[2] In particular, RM through cardiac implantable electronic devices (CIEDs), such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillator or pacemaker (CRT-D or CRT-P), has gained increasing importance due to the implementation of additional algorithms useful in selecting patients with HF at higher risk of HF decompensation, such as the multi-parametric algorithm HeartLogic™ (Boston Scientific, Marlborough, MA, USA).[4] In this paper, we reviewed general aspects of RM in HF patients, the functioning and pathophysiological basis of the HeartLogic™ index, its efficiency in the management of HF patients, and the economic effects and the organizational revolution associated with its use.

Remote monitoring and heart failure

Although initially introduced for complementary evaluation of device functioning, current international guidelines recommend RM as the standard of care (SC) for CIEDs follow-up.[5] Indeed, RM allows earlier detection of clinical problems and technical issues and may allow to better organize in-hospital resources as compared with traditional in-office device checks, which require non-negligible resources consumption in terms of time and specialized personnel involved. The possibility of longer spacing between in-office follow-ups and the need of drastic reduction of in-hospital access during COVID-19 pandemics have fuelled the widespread adoption of RM to replace routine in-office visits. A recent survey assessing the influence of COVID-19 on the RM of CIED in Europe showed a significant increase in the use of RM, with 65% of participants initiating new RM connections for CIEDs implanted before the pandemic.[6] A similar survey on the impact of COVID-19 pandemic on the use of RM was conducted in Italy and showed an increase in the number of patients followed by RM per centre from the year 2012 to 2017, with an exponential increase from 2017 to 2020, thus including the lockdown period associated with COVID-19.[7] Of note, during COVID-19 lockdown, more than one-third of Italian centres reported an increase >30% in the number of CIED patients followed by RM.[7]

To address the unmet need in HF management, several studies have tested RM as a tool in HF patients. The Remote Management of Heart Failure Using Implantable Electronic Devices (REM-HF) randomized 1650 patients with HF and an implanted cardiac device to an active weekly review of RM data or usual care.[8] Rates of death or hospitalization from CV causes did not differ among the groups (*P*-value 0.87), despite an overload of unfiltered data in the RM arm. In the 'MOnitoring Resynchronization dEvices and CARdiac patiEnts' (MORE-CARE) randomized controlled trial, 856 CRT-D patients were allocated to RM controls alternating with in-office visits or in-office visits only.[9] No significant differences were found in the composite outcome of death and CV and device-related hospitalizations between the two groups.[9] These studies showed a neutral impact of RM on the clinical outcome of HF patients, underlying that the increase in the amount of data by itself does not affect clinical outcome, whilst the quality of data and a prompt reaction to a critical interpretation of information can make the difference in terms of outcome. In this regard, the 'Influence of Home Monitoring on the Clinical Status of Heart failure patients'(IN-TIME) randomized controlled study is the only trial demonstrating a significant reduction in mortality among HF patients implanted with ICD or CRT-D followed by daily, multiparametric TM as compared with usual care alone (3% of patients in the RM arm vs. 8.2% in the usual care arm, *P*-value 0.004). In this study, investigators assumed a proactive behaviour, reacting to significant device-detected observation by scheduling an in-person visit or suggesting a patient visit to the family doctor.[10]

Additional functionalities using ICD and CRT devices to detect many physiologic variables were evaluated in the RM setting for early diagnosis and optimal management of HF patients. The Diagnostic Outcome Trial in Heart Failure (DOT-HF) was a randomized controlled study conducted in 335 chronic HF patients implanted with an ICD/CRT-D featuring a tool tracking changes in intra-thoracic impedance.[11] This study did not demonstrate any difference in the composite endpoint of all-cause mortality and HF hospitalizations among the access arm with the impedance information and the control arm (*P*-value 0.063), showing that the evaluation of the intra-thoracic impedance alone is not robust enough to predict an upcoming episode of decompensation. In the 'Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure' (PARTNERS-HF) observational study,[12] an algorithm including patient activity, heart rate, AF burden, Optivol index, the proportion of CRT pacing, and high ventricular rate (HVR) episodes proved to be useful in identifying patients at higher risk of HF decompensation within the subsequent month [adjusted HR 4.8, 95% confidence interval (CI): 2.9–8.1, *P*-value 0.0001].

The HeartLogic™ index: pathophysiological rationale and functioning

Although a variety of sensors in implantable devices may indicate impending HF decompensation, clinical trials using CIED-implemented sensors did not consistently show a reduction in HF hospitalizations. The reasons for the conflicting results obtained in the above-mentioned studies are likely multi-factorial and associated with the complexity of the HF clinical syndrome.[4] From a pathophysiological standpoint, the development of HF decompensation is progressive, with the earliest detectable changes in physiological measurements occurring 10–20 days prior to the onset of symptoms. Indeed, as a response to reduced cardiac output a series of compensatory mechanisms act to maintain organ perfusion, namely the sympathetic nervous system and the renin-angiotensin-aldosterone system.[1] The over-activation of these systems has detrimental effects such as the reduced vascular

compliance due to vasoconstriction, initially leading to raised intra-cardiac diastolic pressures, increased interstitial pulmonary fluid, and lastly fluid retention with weight gain and symptoms requiring HF hospitalizations. The key for the prevention of HF decompensation is the early recognition and treatment of incipient fluid retention because starting treatment when symptoms and clinical signs of HF develop is too late. In this view, the effectiveness of the strategy to prevent HF decompensation strongly relies on finding reliable sensors targeting subtle physiological changes associated with HF pathophysiology and on the right timing of this detection. Recently, efforts have been made to implement CIED with sensors capable to collect data reflecting physiological trends and to combine them into one composite index in a time-fashion manner. A promising example of this approach is the multi-parametric algorithm HeartLogic™ implemented in certain ICDs (with or without CRT) from Boston Scientific.[4] The United States Food and Drug Administration approved the implantation of CIED with HeartLogic™ capability in 2017, and since then the number of HF patients followed by this algorithm has steeply increased. HeartLogic™ is an automatic, remotely managed system combining data obtained from different sensors implanted in the generator into a single score, the HeartLogic™ index. Data directly related to HF pathophysiology are collected: first heart sound (S1), third heart sound (S3), S3/S1 ratio, thoracic impedance, respiratory rate and tidal volume, night heart rate, and patient activity level. In the case of worsening HF, S3 intensity increases as a marker for elevated filling pressures whereas S1 intensity reduces with the reduction of left ventricular contractility, thus resulting in an increased S3/S1 ratio. Intra-thoracic fluid retention as a consequence of raised ventricular filling pressure is associated with a reduction of intra-thoracic impedance and inspiratory volume, with shallower breathing, increased night heart rate, and limitation of physical activity. After CIED implantation, the algorithm is calibrated during a 3-month rolling window during which the baseline HeartLogic™ index is calculated. After this period, significant deviations in one or more sensors relative to the daily variation measured during the calibration period will produce a change in the HeartLogic™ index. HeartLogic™ index is updated every day so that it is possible to describe a trend of its values over time. When the index surpasses a pre-specified threshold, a digital alert is given off in the home monitoring system, the so-called HeartLogic™ alert. The pre-defined threshold value has been set at 16 because this value showed the best diagnostic accuracy in detecting an HF event in the MULTISENSE study.[4] Data coming from the HeartLogic™ algorithm can be transmitted to the caregivers via the manufacturer's specific home monitoring platform (Latitude NXT system, Boston Scientific). Of note, data are automatically transferred by the home monitoring system daily and no alarms are given to the patients unless they are directly contacted by the caregivers.

The hypothesis that data from multiple sensors combined into the HeartLogic™ algorithm would be useful in predicting the risk of HF decompensation was tested in the landmark MULTISENSE trial.[4] In this multi-centre, non-randomized trial of 974 patients with a COGNIS CRT-D (Boston Scientific) affected by HF with reduced ejection fraction and a high functional class or who experienced an HF decompensation in the previous 6 months were enrolled and followed for 12 months for HF events (defined as worsening of HF requiring clinical admission or need of intra-venous medication). The two co-primary endpoints were sensitivity to detect HF events >40% and unexplained alert rate <2 alerts per patient-year. The HeartLogic™ algorithm showed a sensitivity of 70% and specificity of 87.5% with an index value of 16 for predicting HF events and a low unexplained alert rate of 1.47 per patient-year. Interestingly, the index showed a negative predictive value of 99.8% and a median time from alert to HF event of 34 days. A post-hoc analysis of the MULTISENSE trial by Gardner et al.[13] provided further data on the usefulness of the index. Patients with a high baseline index had a 10-fold higher risk of decompensation as compared with patients with an index value <16. Moreover, Gardner et al.[13] demonstrated that the prognostic value of the index was independent from the value of n-terminal pro B-type natriuretic peptide (NT-proBNP): as compared with patients with low NT-proBNP (<1000 pg/mL) and a negative HeartLogic™ index, patients 'in alert' had 24-fold and 50-fold increased risk of HF events at follow-up if NT-proBNP levels were low (<1000 pg/mL) or increased (>1000 pg/mL), respectively.

The HeartLogic™ index: real-world data and ongoing studies

So far, the usefulness of the HeartLogic™ algorithm in real-life clinical practice has been evaluated in few non-randomized studies (Table 1). Capucci et al.[14] described the first experience with the algorithm in clinical practice, publishing a retrospective analysis in a cohort of 58 patients with HeartLogic™ feature implemented CIED. During a median follow-up of 5 ± 3 months, 24 alerts in 16 patients were detected with a rate of 0.99 alerts/patient-year using a nominal threshold value of 16. During the study period, five HF hospitalizations and five unplanned in-office visits for HF were recorded and the HeartLogic™ sensors showed changes in heart sounds in all cases of warnings.[14] In line with the results of the MULTISENSE study,[4] Capucci et al.[14] reported a median early warning time of incipient HF hospitalization of 38 days, whereas the warning time was 12 days in the case of minor events associated with incipient HF deterioration. Interestingly, the authors reported the recovery of the HeartLogic™ index after HF treatment or restoration of an interrupted therapy, proving that the algorithm was effective in the detection of the gradual worsening of HF, enabling action to be taken in patients deteriorating but still not critical. Santini et al.[2] evaluated the HeartLogic™ algorithm implemented within a protocol for the remote monitoring of HF patients in a prospective multi-centre registry. The alert was activated in 104 patients and during a median follow-up of 13 (10-16) months 100 alerts were reported (0.93 alerts/patients-year) in 53 patients. Sixty alerts were considered meaningful and 48 out of 60 alerts (80%) provided new relevant information to the caregivers. Noteworthy, 43 out of 48 (90%) alerts triggered clinical actions, mainly diuretic dosage increase, other drug adjustment or HF hospitalization. The in-alert state was associated with significantly higher rates of any HF signs at in-office evaluation or moderately severe or severe HF symptoms as compared with the 'out-of-alert' state. The incidence of non-clinically meaningful alerts was 0.37 per patient-year, and the rate of HF

Table 1 Main features and results of the MULTISENSE study and real-world studies on HeartLogic™ algorithm

Study	Year of publication	Number of patients	Follow-up (months)	Sensitivity (%)	Specificity (%)	Unexplained alert rate (per patient-year)	Time in alert (% observation period)
MULTISENSE (validation group)[4]	2017	400	12	70	87.5	1.47	17
Capucci et al.[14]	2019	58	5	100	NA	0.41	12
Santini et al.[2]	2020	104	13	69	NA	0.37	15
Treskes et al.[3]	2021	68	12	90	89	0.16	NA
Calò et al.[15]	2021	336	11	NA	NA	NA	11

NA, not available.

hospitalizations associated with an 'out-of-alert' state was very low (0.05 per patient-year). Scheduled monthly remote transmissions resulted in less effective than the alert-based follow-up, allowing the detection of 11 (1%) HF events requiring medical action vs. 43% actionable HeartLogic™ alerts (*P*-value < 0.001). Moreover, this study clearly showed that the alert-based management strategy is more efficient than the scheduled monthly remote follow-up scheme in terms of workload and alert detection timing. Indeed, during the study period 1113 scheduled monthly transmissions (10.3 per patient-year) were reviewed vs. 100 HeartLogic alerts (0.93 patients-year), and the monthly remote data review strategy allowed detection of HF events 14 ± 8 days later than the alert remote data review strategy. In a prospective multi-centre study, Calò et al.[15] evaluated the risk stratification performance of the HeartLogic™ algorithm in a group of 366 patients with ICD and CRT-D in daily clinical practice, describing the management of alerts and its impact on the occurrence of HF events. During a median follow-up of 11 (6–16) months, 273 alerts were recorded in 150 patients (0.76 alerts/patient-year). During the study, 36 HF hospitalizations and 8 HF-related deaths were observed. Thirty-five out of 44 HF-related events were associated with an in-alert state, resulting in an event rate of 0.92/ patient-year, whereas a very low HF event rate of 0.03/ patient-year was observed in the case of an out-of-alert state. In line with the MULTISENSE study showing a warning time of 34 days, Calò et al.[15] described a median time from alert to HF event of 29 days. The in-alert state was associated with a 24-fold increased risk of HF events as compared with an out-of-alert state in a multi-variate model adjusted for potential confounders as AF or chronic kidney disease (HR 24.53, 95% CI 8.55–70.38, *P*-value < 0.001). Of note, 75% of the reported HeartLogic™ alerts were managed remotely and did not require an in-person visit. Similar to the results found by Santini et al.[2], Calò et al.[15] reported that 43% of alerts triggered actions, such as diuretic dosage increase (66%) and HF therapy adjustments (34%) and showed that alerts followed by a clinical action were associated with a significantly lower rate of HF events as compared with non-actionable alerts (HR 0.34, 95% CI 0.12-0.96, *P*-value 0.047). An alert-based remote monitoring was found as effective as in-office management in reducing HF event probability (HR 0.99, 95% CI 0.37-2.68, *P*-value 0.993), underscoring the possibility of managing HF patients without increasing the clinic workload in terms of in-person visits and of scheduled remote transmissions review. Santini et al.[2] described the higher prevalence of severe HF symptoms in the in-alert state as compared with the out-of-alert state. Calò et al.[15] further analysed the clinical implications of symptoms present at the time of HeartLogic™ alert: patients who reported symptoms at the time of HeartLogic™ threshold crossing had a five-fold increased risk of HF events as compared with patients not reporting symptoms (HF 5.23, 95% CI 1.98-13.83, *P*-value < 0.001). Recently, Treskes et al.[3] evaluated the clinical impact of the HeartLogic™ algorithm in terms of reduction in the number of HF hospitalizations in a 1-year post-activation period as compared with a 1-year pre-activation period. Among 68 patients that completed the 1-year follow-up period, the total number of HF hospitalizations declined from 27 in the pre-activation period to 7 in the post-activation period (*P*-value 0.003), and 21 patients were hospitalized for HF decompensation in the pre-activation period vs. 7 in the post-activation period (*P*-value 0.005). A statistically non-significant reduction in hospitalization length duration was observed after the activation of the HeartLogic™ algorithm (7 ± 5 days vs. 16 ± 14 days, *P*-value 0.079). No differences in HF hospitalizations were found among patients receiving CRT therapy during a pre-implantation period and those without CRT or with a CRT implanted more than 1-year before HeartLogic™ activation (*P*-value 0.888), thus excluding CRT-related reverse remodelling as confounding factor in HF hospitalization reduction. Although data obtained in daily clinical practice are promising, these results have not yet been validated in randomized controlled studies. The MANAGE-HF study is a randomized open-label trial that will assess the impact of HeartLogic on all-cause mortality and hospitalizations on 2700 patients with HF randomized to a guideline-directed follow-up with HeartLogic™ monitoring off vs. on.

The HeartLogic™ index: economic impact, resource consumption, and workflow optimization

The latest international guidelines recommend remote monitoring as the SC of CIED patients. However, the introduction of RM in clinical practice is challenging and RM is still largely underused. Essential barriers to its implementation are the lack of reimbursement and the need for
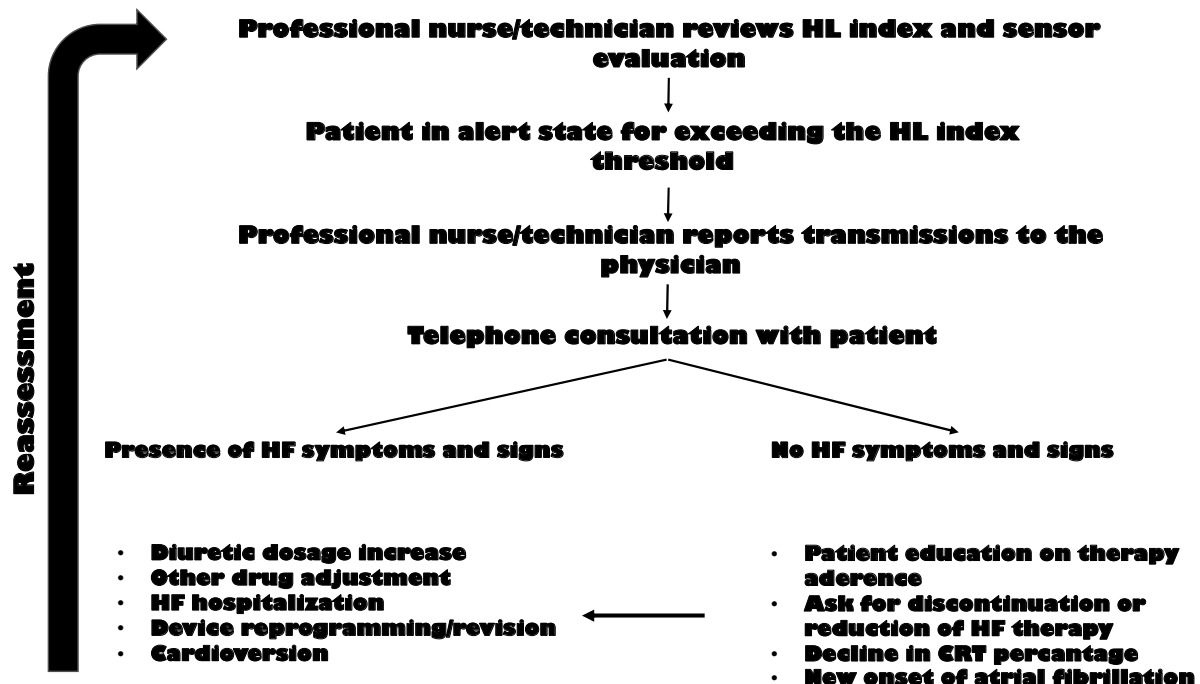
Figure 1 Workflow organization for remote management and follow-up of heart failure patients using the HeartLogic™ algorithm. CRT, cardiac resynchronization therapy; HF, heart failure; HL, HeartLogic.

significant changes in hospitals' workflow and organizational models. From an economic standpoint, current reimbursement models are often not applicable to digital health services and information on the costs and effects of RM interventions is needed to document value for money and to support decision-making. The Health Economics Evaluation registry for Remote Follow-up (TARIFF study) was designed to assess the costs and the benefits of RM as compared with the SC from the perspectives of the healthcare system, patients and caregivers.[16] The overall mean annual cost per patient in the SC was significantly higher than in the RM group (P-value < 0.001), with a reduction of costs of 53.8% in the RM group mainly driven by the reduction in the costs related to CV hospitalizations (P-value 0.003). Similarly, during a median follow-up of 24 months, the MORE-CARE randomized controlled trial[9] showed a significant 38% reduction in the composite endpoint of healthcare resource utilization (including CV hospitalizations, CV emergency department admissions, and CV in-office scheduled or unscheduled follow-ups) for 437 CRT-D patients followed by remote checks alternated to in-office follow-ups as compared with 428 CRT-D patients followed by in-person visits alone (incidence rate ratio 0.62, 95% CI 0.58–0.66, P-value < 0.001). Recently, Treskes et al.[3] reported the economic impact of the HeartLogic™ algorithm based follow-up strategy compared with SC in HF patients. Resource use analysis showed a dramatic reduction in overall health economic costs with HeartLogic™ activation, with a significant reduction in average total cost (P-value 0.003), average hospitalization costs (P-value 0.003), hospital per diem costs (P-value 0.006), and medical imaging costs (P-value < 0.001) per patient. Hence, HeartLogic™ implementation appears associated with a significant reduction

of healthcare costs although additional studies are needed to further confirm these results.

From an organizational standpoint, the integration of RM and HeartLogic™ in routine care implies shifting roles and responsibilities for healthcare personnel and redesigning contemporary healthcare pathways. Moreover, replacing in-office visit with RM requires a cultural change from physicians and co-workers, who are forced to create different relational modalities with the patient and a new organizational model.[17] The organizational model for RM endorsed by current guidelines, the 'primary nursing model' is based on the dynamic interaction between a nurse/technician and a physician. The nurse/technician should educate the patient and its caregivers, activate RM, review daily alerts and transmissions, and report significant transmission to the physician (*Figure 1*). The physician is responsible for reviewing the transmissions/alerts and deciding about their management (follow-ups, call the patients, in-office visits, hospitalizations). The primary nursing model applied to RM was successfully evaluated in the HomeGuide Registry[18] showing that RM was highly effective in detecting and managing clinical events in CIED patients with low manpower and resource consumption. The Home Monitoring Expert Alliance (HMEA) survey recently described the organizational workflow of CIED RM in the Italian clinical practice.[19] The survey was completed by 49 sites and showed that a dedicated organizational model for RM was used in 86% of centres and was based on a primary nursing model in 72% of cases, within a median of two physicians and one nurse per centre. Although 85% of centres provided transmitters before discharge, some sites delivered the transmitter to the patients' home and its activation was supported by a manufacturer external technician.[20] Of note, a direct

collaboration with HF specialists was reported in 51% of centres in the HMEA survey. Indeed, the CIED team managing HF patients should also include nurses and physicians of the HF team, with whom sharing the alerts and transmissions. The presence of a multi-disciplinary team is the crucial point of the RM of HF patients: adequately trained nurses maintain the relationship with the patient and provide support and education, whereas a strong collaboration with HF specialists allows a proactive response to HF alerts to prevent HF events. The daily, multi-parametric evaluation provided by the HeartLogic™ algorithm perfectly fits this organizational model and responds to the need of promptly detecting patients at high-risk conditions, thus enabling an effective resource allocation from patients in a low-risk status (out-of-alert state) to those at high-risk for HF events (in-alert state).

Conclusions

The HeartLogic™ algorithm has shown promising results in daily clinical practice and may serve as a useful tool in identifying patients at increased risk of incipient HF decompensation, allowing time-effective actions to avoid overt HF and hospitalization. The alert-based remote system seems associated with reduced health economic costs without increasing caregivers' workload because it allows to redistribute resources from low-risk patients to high-risk patients. Further diffusion of the HeartLogic™ algorithm in HF daily management will imply the resolution of logistical and financial issues and the adoption of a pre-defined, functional workflow.

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Data availability

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