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Review Article

Remote multiparametric monitoring and management of heart failure patients through cardiac implantable electronic devices

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ABSTRACT

In this review we focus on heart failure (HF) which, as known, is associated with a substantial risk of hospitalizations and adverse cardiovascular outcomes, including death. In recent years, systems to monitor cardiac function and patient parameters have been developed with the aim to detect subclinical pathophysiological changes that precede worsening HF. Several patient-specific parameters can be remotely monitored through cardiac implantable electronic devices (CIED) and can be combined in multiparametric scores predicting patients' risk of worsening HF with good sensitivity and moderate specificity. Early patient management at the time of pre-clinical alerts remotely transmitted by CIEDs to physicians might prevent hospitalizations. However, it is not clear yet which is the best diagnostic pathway for HF patients after a CIED alert, which kind of medications should be changed or escalated, and in which case in-hospital visits or in-hospital admissions are required. Finally, the specific role of healthcare professionals involved in HF patient management under remote monitoring is still matter of definition.

We analyzed recent data on multiparametric monitoring of patients with HF through CIEDs. We provided practical insights on how to timely manage CIED alarms with the aim to prevent worsening HF. We also discussed the role of biomarkers and thoracic echo in this context, and potential organizational models including multidisciplinary teams for remote care of HF patients with CIEDs.

1. Introduction

Heart failure (HF) is currently an important driver of hospitalizations and re-hospitalizations. It is associated with a high risk of adverse cardiovascular outcomes including death, inducing also an important use of human and financial resources [1]. In recent years, systems to monitor cardiac function and patient parameters have been developed with the aim to detect subclinical pathophysiological changes preceding worsening HF. Early detection of subclinical changes is meant to trigger specific decisions and actions, thus possibly preventing subsequent HF hospitalizations [2–6].

In the present review, we will analyze recent data on multiparametric monitoring of patients with HF through cardiac implantable electronic devices (CIEDs). We will provide practical insights on how to timely manage CIEDs alarms with the aim to prevent worsening HF. We will also discuss the role of biomarkers and thoracic echo in this context, and potential organizational models including multidisciplinary teams for remote care of HF patients with CIEDs. For this purpose, Pubmed has been searched from inception to November 2022 using the following search terms in different combinations: alarm, alert, cardiac implantable electronic devices, cardiac resynchronization therapy, decision making, defibrillator, heart failure, multiparametric, remote monitoring, pacemaker. Potentially relevant papers (based on authors' knowledge) and previously published reviews and meta-analyses on this topic were screened as well. The most relevant papers, as judged by the authors, were analyzed and included.

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Table 1
Device diagnostics and algorithms for management of patients with heart failure.
A more extensive version of the table including the name of related clinical studies and the related references in shown in the supplemental material as Supplemental Table S1.
AF, atrial fibrillation; AT, atrial tachycardia; biv, biventricular; HR, heart rate; HRV, heart rate variability; PVC, premature ventricular complex; RM, remote monitoring; S1, first heart sound; S3, third heart sound.

HF diagnostics available at RM (Name of the RM system)	ST Jude/ Abbott Yes (Merlin)	Biotronik Yes (Home Monitoring)	Boston Yes (Latitude)	Medtronic Yes (Carelink)
Monitored patient parameters				
Night heart rate	+	+	+	+
24 h heart rate	+	+	+	+
Heart rate variability		+	+	+
Intrathoracic impedance	+	+	+	+
Heart sounds (S1, S3)			+	
Respiratory rate			+	
Relative tidal volume			+	
Rapid shallow breathing index			+	
Respiratory disturbance index			+	
Activity response	+	+	+	+
AT/AF (burden)	+	+	+	+
Ventricular rate during AT/AF	+	+	+	+
Ventricular arrhythmias	+	+	+	
PVC per day		+		
% Pacing (biv)	+	+	+	+
Defibrillator therapies	+	+	+	+
Sleep incline			+	
Combined score name	CorVue	HeartInsight	HeartLogic	TriageHF
Parameters included in the combined score	Intrathoracic impedance	Night HR, 24 h HR, HRV, intrathoracic impedance, activity response, AT/ AF, PVC per day	Night HR, intrathoracic impedance, heart sounds, respiratory rate, relative tidal volume, activity response	Night HR, HRV, intrathoracic impedance, activity response, AT/ AF, ventricular rate during AT/AF,% pacing (biv), defibrillator therapies

2. Monitoring of heart failure with cardiac implantable electronic devices

Both implantable pulmonary artery pressure monitoring systems, able to remotely transmit data on pulmonary arterial pressure [7], or algorithms based on single or multiple parameters implemented in CIEDs, (e.g.: pacemakers, cardioverter defibrillators (ICDs), or devices for cardiac resynchronization therapy (CRT)) have been developed and tested in several different clinical scenarios [3,4,8–10]. The use of algorithms implemented in ICD or CRT devices has the advantage of avoiding additional hardware, but at present no randomized clinical trial (RCT) demonstrated with certainty a strong clinical benefit in terms of reduced hospitalization rate and mortality [3,8,9,11]. However, interest in this field is still high, with more reliable new technological features being tested and validated [12,13].

Most CIED manufacturers developed their own systems, based on analysis of single or multiple parameters combined in risk scores, as shown in Table 1. A more detailed version including also the main supporting studies is provided in Supplemental Table S1). Some algorithms for managing data derived from HF patients monitoring have shown the ability to predict HF events and worsening HF, with variable predictive accuracy [14–17], thus creating the background for timely decision-making that could prevent clinical worsening.

The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS-HF) study evaluated the potential utility of multiple device diagnostic parameters (intrathoracic impedance, atrial fibrillation burden, ventricular rate during atrial fibrillation, ventricular tachycardia episodes, patient activity, day and night heart rate, and heart rate variability) in predicting HF events [16]. The CIED algorithm, by evaluating changes in these device diagnostic parameters, improved the ability to identify patients at risk of HF events in a 30-day period, with possibility to classify patients as exposed to a high, medium, or low risk of HF events [18,19]. In a study prospectively enrolling 100 HF patients (TRIAGE-HF study), it was shown that high device-generated HF risk status was associated with symptoms of worsening HF in 63% of cases, with intrathoracic impedance as the most frequently altered parameter [20]. Actions were taken in 54% of high-risk alerts. High device-generated HF risk status showed good sensitivity (98.6%) and average specificity (63.4%) in identifying worsening HF events [21].

The HeartLogic™ algorithm (Boston Scientific, St. Paul, United States) includes the largest set of monitored parameters and is implemented in ICD and CRT-D devices. It considers five sensors to detect impending HF decompensation [11,14] including first and third heart sounds (S1 and S3, respectively) and the S3/S1ratio, respiration rate, intrathoracic impedance, heart rate during the night and monitors the amount of physical activity. The automatic integration of these parameters results in the HeartLogic™ index and a threshold of 16 (nominal value) triggers an alert for impending decompensation. The index is patient-dependent and is based on measurements performed on a daily basis that are compared with a reference index, calculated over a 3-month rolling window. HeartLogic™ was tested in MultiSENSE study [14] in a population of 900 HF patients implanted with CRT-D devices. Alerts triggered by a HeartLogic™ index value of 16 had a sensitivity of 70% (95% confidence interval, CI: 55.4% to 82.1%) for HF events (HF admissions or unscheduled visits requiring intravenous treatment) with an unexplained alert rate of 1.47 per patient-year (95% CI: 1.32 to 1.65). The median time between an alert and the following HF event was 34.0 days (interquartile range: 19.0 to 66.3 days). HeartInsight is a recently developed algorithm obtained by multiparametric CIED remote monitoring. These parameters were combined with the Seattle HF Model (based on demographic, clinical, therapy, blood, and urine data) that was used as a baseline risk-stratifier, aiming as potentially improving the predictive power. In the SELENE-HF study, 918 ICD or CRT-D patients were enrolled and randomly allocated the algorithm derivation group or algorithm validation group. In the former group the area under the

Receiver Operating Characteristic curve for HF hospitalization was 0.89, and in the latter sensitivity of predicting HF hospitalizations was 65.5% with 0.69/patient-year false alert rate. When the Seattle HF model was removed from the algorithm, sensitivity did not change, while false alert rate increased to 0.76/patient-year [15].

The temporal dynamic of changes that usually occur before an HF event are shown in Fig. 1 and, despite some inter-patient variability, their analysis is important to understand how to integrate CIED diagnostics with optimized patient management [22].

The first and third heart sounds are monitored by mean of an accelerometer that is located in the CIED pulse generator and measures the movement of the right ventricular wall in diastole via the right ventricular lead. These movements follow a wave-type pattern correspondent to heart sounds heard at auscultation and are registered by the device in the form of S1, S3 and S3/S1 ratio [11]. Detailed description of heart sound detection by CIEDs and their outcome implications are discussed in detail in a dedicated section in the Supplementary material.

Intrathoracic impedance is derived by the vector between the right ventricular lead and the device and is decreased in case of increase in intrathoracic fluids such as in pulmonary congestion [19,23]. The respiratory rate and tidal volumes are the result of an analysis made by the device on thoracic impedance, as result of low voltage shocks delivered. Variation in device detected respiratory rates were found associated with the risk of worsening HF [24]. Heart rate is continuously monitored and specifically heart rate during the night has a significant role. Finally, the level of patient activity can be monitored by the accelerometer of the CIED.

3. Clinical significance of CIED alerts and subsequent clinical actions in heart failure patients

The potential clinical value of alerts from a CIED, when triggered by changes in a series of parameters potentially predictive of HF decompensation, is strictly linked to a series of factors, that should be carefully considered when contacting a patient after an alert:

- the positive predictive accuracy of the alert in the specifically monitored population;
- the time interval elapsed between the alert and patient contact;
- some patient related factors (adherence to physician's advices and prescriptions, inability to recognize some HF symptoms, empowerment, willingness to be involved in the care process, caregiver, etc.);
- the consequent decision-making and the actions put in practice by the physicians.

The Multiple Cardiac Sensors for Management of Heart Failure (MANAGE-HF) study was a single arm, open-label study based on management of HeartLogic™ alerts according to an "alert management guide" designed to evaluate HeartLogic™ integration in clinical practice, in order to improve outcomes with a favorable safety profile [25].

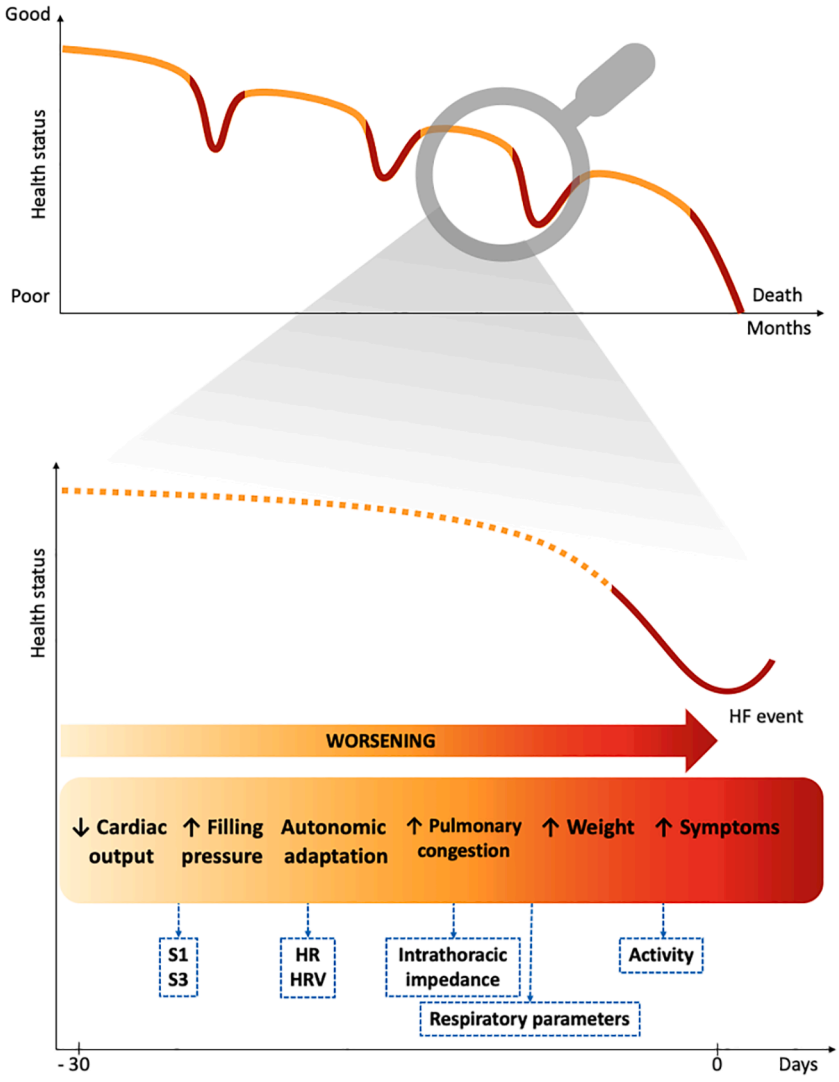

Fig. 1. Clinical trajectories of heart failure. Top panel shows long-term trajectories of patients with multiple events of heart failure decompensation. Bottom panel shows the trajectory of a single event of heart failure decompensation occurring in a certain time of the clinical course and the underlying pathophysiological changes occurring in the preceding 30 days. These changes can be detected by multisensory monitoring of heart failure through cardiac implantable electronic devices. CIED, cardiac implantable electronic device; HF, heart failure; HR, heart rate; HRV, heart rate variability; S1, first heart sound; S3, third heart sound.

According to the study design, health care providers received automated notice when an initial HeartLogic™ alert occurred and were required to attempt to contact the patient, for adopting the advised alert management guide. Moreover, they received weekly reminders (re-alerts) until the HeartLogic™ index recovered below the nominal alert recovery threshold. In detail, in case of an alert the guide advised to contact patients by phone within 3 days and initiate a qualified treatment. If no treatment was initiated, over the phone, participating sites were instructed to evaluate the patient in clinic, for safety concern. After assessment of potential triggers, the advice was to escalate treatment, up to a reassessment in a week of persistence/reduction/resolution of the HeartLogic™ index that characterized the alert. It is noteworthy that absence of signs or symptoms of HF was not considered a reason for not proceeding with escalation, apart obvious clinical contraindications. However, according to the last version of the guide that was elaborated and distributed to participants, in case of alert physicians had to choose one or more of different options, i.e.: 1) augmentation of decongestive treatments, in terms of increase in diuretic dosage/ regimen or start/ up-titration of angiotensin receptor neprilisin inhibitors (ARNI); 2) address precipitating factors of the alert (atrial fibrillation, anemia, ischemia, recent reduction of HF drugs, etc.); 3) optimize guideline-directed medical therapy for HF (angiotensin converting enzyme inhibitors (ACEi)/ Angiotensin receptor blockers (ARB) [26], ARNI, beta-blockers, mineralocorticoid receptor antagonists (MRA), or hydralazine and nitrates). The implementation of this guidance into practice showed marked variability across sites, both in alert response rates and treatments, the latter ranging from increasing diuretics only (loop or thiazide), to increase diuretic and non-diuretic HF medications (beta-blockers, ACEi/ARB/ARNI, MRA, vasodilators), to increase non-diuretic HF medication only, or not increase any HF treatment. It is noteworthy that diuretics were more frequently used initially, with movement toward more sustained diuretic changes and the addition of non-diuretic HF medications as the alert cases progressed [25].

This study deserves in our view a series of considerations, taking into account that it is important to distinguish between cases where, at the time of patient contact after an alert, the patient actually has new symptoms and cases where the alert is truly pre-symptomatic, since no new symptoms (in particular no symptoms of congestion) are reported by the patient. In this study, the increase of diuretics regimen was the principal treatment adopted in response to alerts and this resulted in a shorter alert duration. It is noteworthy that guideline-directed medical treatment (ACEi/ARB/ARNI) was not usually increased after alerts [25]. Similarly, in the INTERVENE-HF study, 66 HF patients with reduced ejection fraction implanted with CRT-D embedding the TriageHF risk score feature were prospectively followed for approximately 8 months. 49 HF alerts were generated and 26 of them underwent a standardized 3-day course of diuretic up-titration that led to $a \geq 70\%$ recovery of intrathoracic impedance toward baseline levels in the majority of cases [27].

Diuretics are the cornerstone of decongestive therapy and appropriateness of their use implies that congestion is diagnosed according to various methods clinically available, whose sensitivity is variable [28]. The aim of diuretic therapy or intensification of diuretic regimen is first to relief symptoms (dyspnea in particular) and secondly to improve congestion. Therefore, according to current status of knowledge, there is not an established role for preventing symptoms of congestion in asymptomatic patients. There are reports based on observational data suggesting that routine use of diuretics may actually be associated with adverse outcome at mid- or long-term [29]. A more detailed discussion on the use of diuretics and related outcomes in HF patients is reported in a dedicated section of the Supplementary material. As a corollary, the prescription of diuretics in the absence of detectable signs of congestion, even with subclinical parameters suggesting its development, corresponds to a setting where the role of diuretic therapy is undefined at present. For this reason, in the absence of clinical signs of congestion, decision-making in reaction to an alert of impending HF generated by a CIEDs with multiparametric monitoring should strongly consider, in our view, the possibility of escalating disease-modifying agents, such as ARNI, ACEi/ARB, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, rather than increase in diuretics, in line with the marked benefit on outcomes demonstrated for all these agents [26].

According to data from MultiSENSE study [14,30], the time between an alert and the occurrence of an HF event, frequently leading to HF hospitalization, is a time that should be characterized by a decision making targeted to avoid the event (Fig. 1). The fact that the benefit of sacubitril/valsartan, enalapril, eplerenone, and SGLT2 inhibitors can be observed already in a time frame of 10–20 days [31,32], strongly supports in our view, in case of an alert without overt clinical congestion, to consider escalating disease modifying agents (sacubitril/valsartan, ACEi/ ARB, SGLT2 inhibitors), through implementation or up-titration, as an alternative to diuretic prescription as a default option. In the setting of overt acute heart failure and hospitalized patients, the STRONG-HF study [33] clearly demonstrated that an intensive treatment strategy of rapid up-titration of guideline-directed medications (targeted to up-titration of treatments to 100% of recommended doses within 2 weeks of discharge), coupled with a close follow-up significantly reduced HF symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or HF readmission compared with usual care and was also well accepted by patients. It will be of great importance to assess in the next future if up-titration of optimized medical therapy, found effective in patients with overt, clinically manifest HF, will be beneficial even when HF is in a pre-clinical stage, as it may happen when an alert is derived from multiparametric HF monitoring in the absence of overt HF.

4. Potential role of BNP, NT-proBNP, and thoracic echo in patients with alerts for suspected cardiac decompensation

Brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) concentrations allow to quantitatively assess the presence and severity of hemodynamic cardiac wall stress and HF. Their role is well established as prognostic markers in HF patients and in discriminating HF from other causes of dyspnea, but this is not yet the case for guiding HF treatment [34,35]. Moreover, they do not constitute pure and exclusive markers of left ventricular dysfunction. Indeed, a series of structural and functional cardiac abnormalities may lead to increased BNP or NT-proBNP levels, including left ventricular diastolic dysfunction, right ventricular dysfunction, increased pulmonary pressures, and atrial or ventricular tachyarrhythmias [36].

The contribution of BNP in the setting of patient with HF at home was evaluated with regard to prediction of hospitalizations for acute HF exacerbation and outcome in a multicenter, single-arm, double-blinded observational prospective clinical trial including daily monitoring of BNP [37]. This study, based on daily monitoring of BNP on drops of finger-stick blood, found that daily BNP could change on any patient-day and that the hazard ratio per unit increase of BNP was 1.84 (95% CI: 1.42 to 2.39). A subsequent post-hoc analysis of the same trial showed that, in patients with HFrEF, rapid rise in BNP >200 pg/mL failed to predict acute HF decompensation, while it was predictive in patients with HFpEF [38]. It has been shown that a serial change in BNP of ≥100 pg/ml had a sensitivity of 47% as compared to a sensitivity of only 9% for ≥2 kg weight gain over a period of 2–3 days with regard to prediction of HF decompensation, as clinically assessed, which is a potential advantage in term of early diagnosis [39].

In this context, BNP or NT-proBNP and CIED multiparametric risk prediction scores may be combined to improve HF event prediction after a CIED alert. Gardner et al. found that the combination of high NT-proBNP at baseline (>1000 pg/Ml) and HeartLogic™ alert was able to identify periods of time with a 50-fold increased risk of worsening HF, thus further improving the prediction associated with HeartLogic™ alerts, which per se is associated with a 10-fold increased risk of worsening HF [40]. There is also the possibility to combine the information of

a CIED alert with an assessment of the change of NT-proBNP, taking into account the delta change as compared to a prior value, in order to improve the predictive implications for HF decompensation, but this has not been formally tested. Of note, in order to correctly interpret natriuretic peptides' fluctuations, spontaneous biological variability of blood biomarkers should be kept in mind. According to literature, only changes of at least 40% for BNP and 25% for NT-proBNP levels have to be considered clinically relevant, since smaller changes are in the range of spontaneous biological variability [41]. Resampling of NT-proBNP may be planned 2 to 4 weeks after disease-modifying agent escalation, and it is also associated with prognostic implications [41]. Even with these limitations, BNP/ NT-proBNP levels have a potential role for integrating and interpreting in clinical terms the information provided by multiparameter monitoring of HF through CIED and guide decision-making even in the early phases.

Since the sequence of events leading to symptomatic pulmonary congestion in HF can be conceptualized as a cascade (Fig. 1), lung ultrasound has been tested for enhancing early detection of extra-vascular lung water, even in a pre-clinical stage [42]. Indeed, studies on lung ultrasonography showed that B-line changes can be present in the absence of symptoms, and therefore this finding has been reported to anticipate by hours or days the occurrence of acute dyspnea in HF [43]. It is noteworthy that only 20%–30% of patients with HF and B-lines have crackles on pulmonary auscultation [44,45]. Specific protocols for lung analysis with ultrasonography have been published, suggesting evaluation of 28 points[46–48] that allow a quantitative assessment of decompensation [49]. Simplified protocols have been proposed and adopted in practice as well [50,51]. B-lines detected by lung ultrasound were found to allow good prediction of pulmonary congestion indicated by extra-vascular lung water, but not by pulmonary capillary wedge pressure [48,52]. The prevalence and clinical significance of subclinical congestion has been assessed also in patients with at least one clinical risk factor for HF (diabetes, ischemic heart disease, or hypertension) by applying three ultrasound criteria: inferior vena cava diameter (IVC), jugular vein distensibility (JVD) ratio (the ratio of the jugular vein diameter during the Valsalva maneuver compared to the diameter at rest) and the number of B-lines from a 28-point lung ultrasound examination. The presence of congestion was defined as IVC diameter $>$ 2.0 cm, JVD ratio $<$ 4.0 or B-lines count $>$ 14 and subclinical congestion prevalence (at least one of the previous criteria) was 30% (13% by inferior vena cava diameter, 9% by jugular vein distensibility ratio and 13% by B-line quantification respectively) [53,54].

These data suggest that lung ultrasound and inferior vena cava evaluation can be considered in patients with CIED alerts triggered by multisensory diagnostics, in order to provide clinical clues on presence/ absence of sub-clinical signs of pulmonary or systemic congestions [55, 56].

5. Flowchart for decision making in CIED patients under remote monitoring

The extensive diagnostic capabilities of CIED that are currently available to monitor patients' status have dramatically changed the scenario for remote monitoring, implying a shift from a strictly device-centered follow-up to perspectives focused on the patient and its conditions with regard to stability or worsening of HF status [2–4]. In the future, this may translate in better health care delivery and clinical outcomes in the field of HF, but requires appropriate organization of care at different levels, involving the health care systems (including appropriate reimbursement practices) [6], as well as hospitals and cardiology services, which should define specific pathways for appropriate management of the flow of data that are remotely transmitted from CIEDs [57]. The management of HF patients with CIED is complex and multidisciplinary. Data (and alerts) gathered through CIEDs are remotely transmitted to a platform that can be accessed by the remote monitoring team. After accurate data revision and interpretation, the first step of the decision-making process involves contact with the patient/ caregiver and remote patient evaluation (Fig. 2). CIED derived parameters should be integrated with medical history and clinical and laboratory findings. If no signs or symptoms of impending or worsening HF are found, a check of natriuretic peptides levels (BNP or NT-proBNP) particularly in case of an alert persisting for 2–3 weeks may be considered to improve the specificity of the alert, to guide therapeutic choices, or to suggest additional diagnostic evaluations. Periodic assessment of natriuretic peptides may not be a feasible option for routine patient monitoring at home. However, it would be important to provide every patient discharged after an HF hospitalization with pre-discharge levels of BNP or NT-proBNP (the latter to be preferred for patients treated with sacubitril/valsartan). Additionally, it might be useful to assess BNP or NT-proBNP in patients with CIED in stable conditions as reference for subsequent evaluations during follow-up, including evaluation of CIED alerts and clinical events in an integrated way. The challenge for physicians is to take the appropriate decision at the right time, and at present this appears easier for managing device alerts as compared to alerts related to HF. Indeed, after contacting the patient, there are several possible clinical scenarios and actions that can be taken including (but not limited to) a wait and see approach, plan further investigations, change medications, plan a visit, or even a hospital admission.

6. Multidisciplinary team management

The implementation of CIED remote monitoring in clinical practice requires specific organizational models and teamwork among all health care professionals involved in multidisciplinary care of HF patients, with the aim to reduce mortality and hospitalizations and improve quality of life [2,4,58].

In the setting of CIED remote monitoring of HF patients, cardiologists, HF specialists, electrophysiologists, allied professionals (e.g.: HF/ electrophysiology nurses, cardiology technicians, etc.) and eventually general practitioners (GPs) may all play a specific but integrated role. The physician that advised use of remote monitoring, according to guidelines [4,12,58,59], is usually in charge of patient monitoring. However, remote monitoring team composition, responsibility and organization can vary between countries, hospital, centers, and settings. Thus, a multidisciplinary patient management should be organized according to local regulations and resources. In some contexts, physicians are in charge of the whole remote monitoring process, while in others they review data that have been previously screened by a cardiology technician or specialized nurse adequately trained to correctly evaluate, prioritize, and manage remote monitoring alerts [60]. Once an actionable alert has been identified, they usually notify a referring electrophysiologist or cardiologist after quickly ruling out life-threatening events such as ventricular tachyarrhythmias and shock therapy, or technical issue related to device (e.g.: inappropriate detection of arrhythmias due to oversensing of signals/noise, lead disfunction, lower biventricular pacing percent stimulation in CRT, etc.). The consequent decision usually implies to contact the patient/ caregiver for having feedback on actual patient's status (Figs. 2 and 3). A careful remote patient evaluation is performed through screening questions (Fig. 2) and, according to the specific causes that triggered the alert and the clinical conditions of the patient, the best management strategy is shared among the multidisciplinary team. Some clinical decisions may be taken by the physicians remotely, while other require an in-person evaluation. GPs may play an important role, if a plan of collaboration has been established with the hospital physicians, for the first in-person patient evaluation after a persistent alert ($>$2 weeks) and eventually for the prescription of laboratory tests, investigations (e.g.: echocardiogram or thoracic echography), or changes in medication. An in-hospital visit or a hospital admission can be programmed if needed, particularly in presence of any symptom or sign of HF [61]. In Fig. 3, we present a flowchart related to possible scenarios and steps for appropriate decision-making in patients with CIEDs involving remote monitoring of HF, taking care

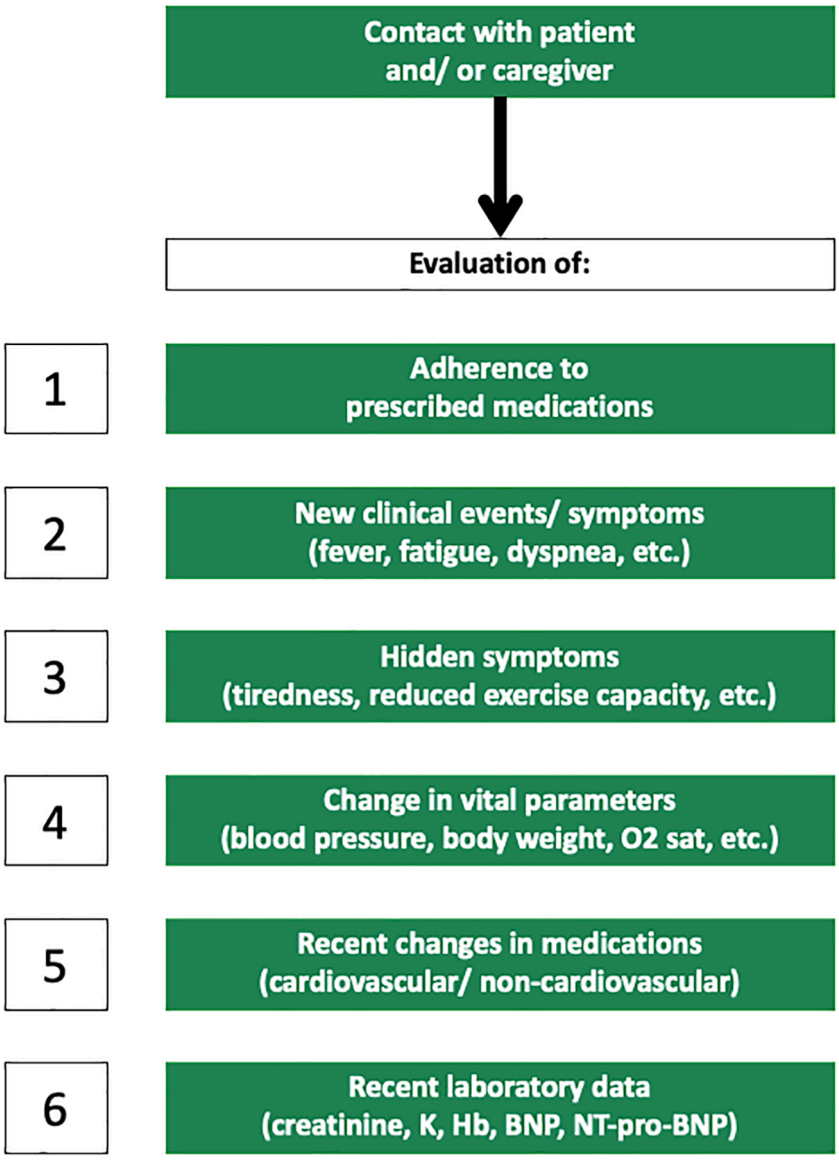

Fig. 2. Parameters that should be evaluated when contacting a heart failure patient after an alert prompt by a cardiac implantable electronic device. BNP, brain natriuretic peptide; Hb, hemoglobin; K, potassium; NT-proBNP, N-terminal pro b-type natriuretic peptide; O2 sat, oxygen saturation.

of both device and patient problems, in an attempt to reduce hospitalizations and improve outcomes.

As a matter of fact, the COVID-19 pandemic strongly enhanced a wider implementation of remote care[62–65] in order to re-design the organization of health care systems, especially for chronic diseases such as HF [66,67]. Patients with CIEDs have the advantage of carrying the hardware for remote monitoring, thus minimizing the cost and organizational problems that remote monitoring implies when using external devices. In consideration of the increasing burden of HF, linked to progressive aging of the population, it is topical to sustain strategies for implementing remote monitoring in HF patients carrying a CIED with the aim to maximize the possibility of optimized medical therapies for reducing hospitalizations and improving patient outcomes.

7. Future directions

Whether remote monitoring reduces mortality and hospitalizations in patients with HF as compared to standard care is still matter of debate [4,68]. At present, only one randomized controlled trial showed that automatic, daily, multiparameter telemonitoring through CIED improved clinical outcomes as compared to usual care [69]. At 1 year, patients in the telemonitoring arm had less odds of worsening of a composite of all-cause death, overnight hospital admission for HF, change in NYHA class, and change in patient global self-assessment (odds ratio 0.63, 95% CI 0.43–0.90). The difference was mainly driven by reduced mortality in the former arm (3% of patients, vs 8.2% in usual care arm, $p = 0.004$), while hospitalizations for worsening HF were not significantly different. A sub-analysis of the trial [70] showed that CRT-D patients had more frequently a worsened score at study end as compared to ICD patients. However, the prevalence of improved score after 1 year was higher in CRT-D patients and telemonitoring was associated with a greater benefit in the CRT-D subgroup than in ICD subgroup (absolute mortality reduction 6.8% vs 2.9%). CRT-D patients were significantly older, sicker, and with a lower left ventricular ejection fraction than ICD recipients. They generated more telemonitoring alerts, more triggered contacts, and additional follow-up visits. In this context, it may be possible that the higher risk population benefited the most of telemonitoring for the widest margin of intervention they could get. On the other hand, some studies showed remote monitoring had neutral effects on hard outcomes as compared to usual care [71,72]. Of note, a

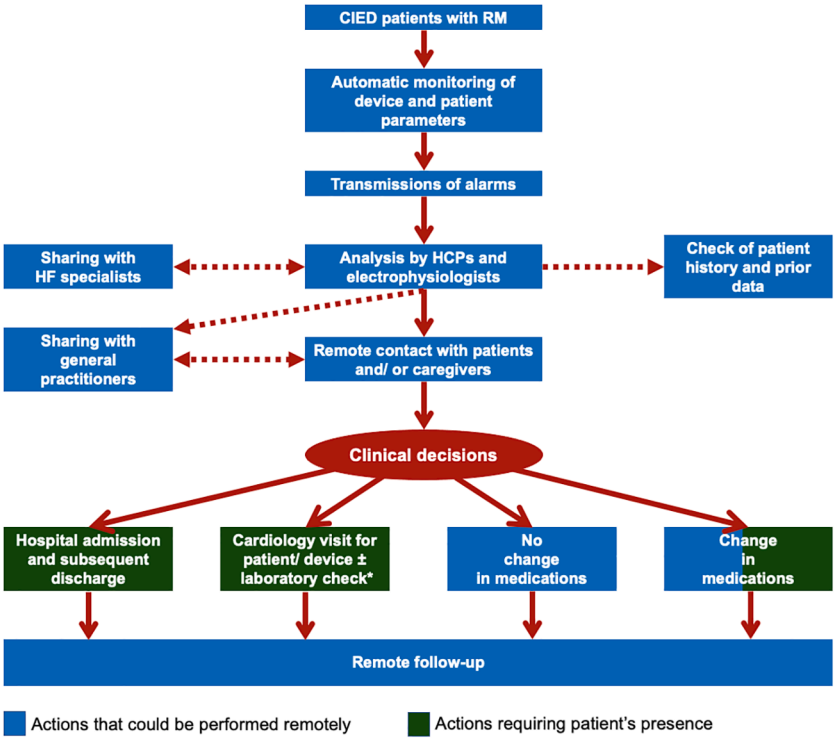

Fig. 3. Possible scenarios and steps for appropriate decision-making in patients with CIEDs involving remote monitoring of heart failure, taking care of both devices' and patients' problems, in an attempt to reduce hospitalizations and improve outcomes.
CIED, cardiac implantable electronic device; HCPs, health care professionals; HF, heart failure; RM, remote monitoring.
*In-hospital or outpatient setting according to local organization of cardiology care.

randomized study conducted on 335 chronic HF patients implanted with an ICD/CRTD featuring a monitoring tool capable of tracking changes in intrathoracic impedance showed a higher risk of HF hospitalization in the remote monitoring arm than in the control arm (HR=1.79; 95% CI, 1.08–2.95) [73].

While sensitivity of multiparametric CIED alerts in predicting HF events is high, specificity is still suboptimal, potentially generating a higher number of visits and hospitalizations than usual care. In the MultiSENSE study [14], false positive rate was 1.56 (95%CI: 1.41–1.77), specificity was 85.7%, and an unexplained alert rate was 1.47 per patient-year (95%CI: 1.32–1.65). The specificity reported in the Triage-HF plus [21] was 63.4%, 28% of patients with a high-risk alert had no apparent cause for the high score and 14.9% had an acute medical condition other than worsening HF. Indeed, current HF guidelines do not grant a high level of recommendation for remote monitoring in HF patients (Class IIb, level of evidence B) [59].

Finally, the cost-effectiveness of remote monitoring of CIED in HF patients is still unclear. Few studies addressed this issue and they are heterogeneous. It appeared that reduction in number of visits was the economic beneficial effect of remote monitoring more robustly observed. On the other hand, time and workflow issues with remote patient management were substantial [74]. In the MORE-CARE randomized trial [23,75], a significant 38% reduction in the use of healthcare resources in favor of the remote monitoring group was observed, mainly as a result of a decrease in-office visits. This finding was later confirmed by a meta-analysis of 11 randomized controlled trial showing a reduction in total number of visits and lower monetary costs (despite more unplanned hospital and emergency room visits were observed) [8]. However, the economic impact of remote monitoring analyzed using outcome measures is complex and still needs clarification.

For these reasons, there is need to invest in planning both randomized trials and pragmatic studies evaluating the effectiveness of physician's decision making on the basis of remote monitoring alerts, as well as evaluating the implementation and organization of cardiology services taking care of remote monitoring of HF patients carrying a CIED, in line with the approaches of health technology assessment [76]. Accurate cost-effectiveness analyses are needed as well in order to assess whether the organizational investment has a positive return.

8. Conclusions

Several parameters derived by CIED continuous monitoring can be combined in multiparametric scores reliably predicting patient's risk of worsening HF. Early detection of pre-clinical changes may potentially lead to early patient management, even days or weeks before overt decompensation. The sensitivity of multiparametric monitoring of HF through CIEDs was found reliable, but the specificity is still suboptimal. In case of alerts received by remote monitoring, it is needed to contact the patient in order to have feedback on presence/ absence of overt or hidden HF symptoms. This action should be followed by decisions on patient management that may range from clinical, laboratory or instrumental checks, including also echocardiography and biomarkers, in order to assess the need for medical therapy changes (by escalating disease-modifying medications or, rather, increase diuretics) or, in some cases, the need for planning an outpatient visit or a hospital admission for a complete re-evaluation and early treatment before a more severe HF decompensation.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.04.011.

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