Rationale and Design of the Multisensor Chronic Evaluations in Ambulatory Heart Failure Patients (MultiSENSE) Study

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ABSTRACT. Heart failure is associated with exacerbations leading to hospitalization. In the United States, over 1 million heart failure hospitalizations occur annually, and nearly one-fourth of patients are readmitted within 30 days. Accordingly, a search has ensued for methods to detect worsening heart failure at an early stage where corrective therapy is simple. Implantable devices are often used in patients with heart failure, and are equipped with sensors that can be used to monitor physiologic parameters reflective of heart failure status. The use of sensors indicative of multiple physiologic parameters may facilitate more effective patient management. The Multisensor Chronic Evaluations in Ambulatory Heart Failure (MultiSENSE) study will evaluate the ability of multiple implantable device sensors to reflect early subclinical signs and symptoms of worsening heart failure. The objective of the study is to develop multisensor algorithms that provide early warning of worsening heart failure to facilitate intervention. The study will enroll up to 990 subjects with an existing device and enable additional sensor data collection, including respiration, heart sounds, thoracic impedance, and activity response measurements. Clinical patient data including heart failure exacerbations will be collected and association with sensor data will be evaluated. Sensors will be systematically evaluated individually to determine the strongest indicators of worsening heart failure and in combination to develop improved indicators of patient status. Implantable electronic devices are often used in the treatment of heart failure, and have sensor capabilities that may be expanded to monitor physiological changes indicative of worsening heart failure.

KEYWORDS. heart failure decompensation, remote monitoring, sensor diagnostics.
HF hospitalizations and readmissions still remain a major clinical problem. A number of telemonitoring strategies have been evaluated to identify early indications of worsening HF when corrective action is simple. Daily weight monitoring is a straightforward method to detect short-term changes in volume, but a significant weight increase is absent in half of patients hospitalized for HF.\textsuperscript{11,12} Implantable hemodynamic monitoring has shown that pulmonary artery pressure increases prior to worsening HF events, but these devices require a dedicated implant or lead.\textsuperscript{13–15} In contrast, sensors (and associated remote monitoring capability) within implanted cardiac therapy devices have the advantage of not requiring additional implants. Some of the existing implanted diagnostics have been assessed for detection of worsening HF.\textsuperscript{12,14,16–20} Indirect measurement of thoracic fluid from implantable device lead impedance shows early changes prior to worsening HF, but its detection performance as a single sensor has been limited.\textsuperscript{17} Similarly, combining device diagnostics that are not specifically designed for HF monitoring such as heart rate, heart rate variability, activity, and atrial arrhythmia burden have had limited detection performance.\textsuperscript{12}

Given the complex etiology of worsening HF and the limited value of any one individual clinical sign, symptom, or laboratory measurement, it is standard clinical practice not to interpret these in isolation, but rather in the context of all available clinical data. Similarly, our hypothesis is that monitoring multiple judiciously selected sensor signals associated with worsening HF in combination with a multisensor detection algorithm will provide superior performance over any single sensor alone. Although some sensors are available from implantable devices to predict an HF event (such as intra-thoracic impedance), they have not received widespread use because of performance of the parameter. It is anticipated that a more comprehensive assessment of the risk of an HF event will lead to greater clinical use and may be useful in guiding the treatment of HF patients.

The MultiSENSE Chronic Evaluations in Ambulatory Heart Failure (MultiSENSE) study will evaluate the following implanted sensor measurements designed to measure physiological variables that are closely associated with signs and symptoms of worsening HF: 1) respiration (respiratory rate and relative tidal volume) measured via intra-thoracic impedance; 2) physiologic response to activity measured from relationships between respiration and heart rate to activity determined during activities of daily living; 3) thoracic fluid measured using multivector intra-thoracic impedance; and 4) heart sounds (including the third heart sound) measured from mechanical vibrations using the device accelerometer.

Methods

Study overview

The MultiSENSE study (www.clinicaltrials.gov NCT 01128166) is a multicenter, international, prospective, non-randomized, feasibility study designed to evaluate the ability of multiple sensor measurements derived from a cardiac resynchronization therapy defibrillator (CRT-D) to detect signs of worsening HF. The objective of the study is to develop algorithms that facilitate early detection of worsening HF. An enrollment ceiling of 990 subjects from up to 120 worldwide centers is expected to provide approximately 100 HF events usable for algorithm development and validation.

Patients

Subjects who have an existing COGNIS\textsuperscript{®} CRT-D pulse generator (PG) (Boston Scientific, St. Paul, MN) will be recruited for the study. Following enrollment, subjects will have their device converted to an investigational Sensor Research Device (SRD-1) no earlier than 30 days post implant and no later than 44 days post enrollment. After conversion subjects will be followed for a maximum of 12 months. At the end of 12 months, the subject’s device will be reconverted back to a market-approved COGNIS device. Following reconversion the subject will have one final study visit (within 40–44 days after reconversion). Subjects who meet the study eligibility criteria (Table 1) and do not have any exclusions will be recruited only after providing written informed consent approved by the investigator’s Institutional Review Board/Ethics Committee. Subjects with a history of cardiac arrhythmias are eligible for enrollment with two exclusions that are related to the device conversion process. Subjects who are pacemaker dependent, or who have experienced appropriate tachycardia therapy for arrhythmias <165 bpm within the previous week are excluded. This exclusion is due to modifications to device therapy that occur during the device conversion to an SRD.

During that time window, tachycardia therapy is limited, and there can be up to a 5-s pause in bradycardia pacing therapy. To further mitigate any potential risk, surface electrocardiogram monitoring is required in an environment where external safety equipment including a defibrillator is present, and the study investigator must be present during the conversion. Beyond these specific exclusions, the study population is intended to include subjects with the range of arrhythmias experienced by the device HF population. This includes subjects with a prior history of arrhythmias and subjects who develop arrhythmias during the course of the trial. The device programming for arrhythmia therapy will be per standard practice, and will not be controlled in this trial. Subjects with a device left ventricular (LV) sensitivity <0.7 mV are excluded to prevent potential LV oversensing of intra-thoracic impedance measurements in special cases, such as the VDD pacing mode when no atrial senses are detected. LV offsets may not be programmed >0 in this trial because that functionality is unapproved in some study geographies.

Devices

The SRD-1 system consists of two primary components: a COGNIS CRT-D PG modified by the download of
Table 1:

Inclusion criteria

- Age 18 or above, or of legal age to give informed consent specific to state and national law
- Willing and capable of returning to the investigational center for all follow-up visits and emergency care
- Willing to participate in all testing associated with this clinical investigation
- Currently implanted with a CRT-D system including a COGNIS device (model N119, N120, P107, or P108) with right atrial (RA), right ventricular (RV), and left ventricular (LV) leads
- Classified as NYHA (New York Heart Association) Class II, III or IV within the last 6 months

Exclusion criteria

- Inability or refusal to sign the Subject Informed Consent
- Inability or refusal to comply with the follow-up schedule
- Documented as pacemaker-dependent
- Unable to rest comfortably in a semi-recumbent position for up to 20 min
- LV sensitivity programmed to less than 0.7 mV automatic gain control (AGC)
- Subjects that have a history of appropriate tachycardia therapy (external or implanted) for rates < 165 bpm within 1 week prior to enrollment
- Device battery status indicates approximate time to explant < 2 years
- Likely to undergo lead or PG revision during the course of the study as determined by the investigator
- Receiving regularly scheduled intravenous (IV) inotropic therapy as part of their drug regimen
- Subjects that have received a heart or lung transplant
- Receiving mechanical circulatory support
- Subjects who have been referred or admitted for Hospice care
- A life expectancy of less than 12 months per physician discretion
- Subjects whose devices have previously been converted to the SRD-1 and withdrawn from this study
- Women who are known to be pregnant or plan to become pregnant within the course of the study
- LV offset is programmed to a value greater than zero
- Implanted with active Medtronic Fidelis lead models: 6930, 6931, 6948 or 6949
- Currently implanted with unipolar RA, RV, or LV leads
- Enrolled in any concurrent study, without Boston Scientific written approval
- Subjects who have received a sub-pectoral COGNIS implant (with specific model numbers)
- Subjects that have a history of appropriate tachycardia therapy (external or implanted) for rates > 165 bpm within 1 week prior to enrollment
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The four configuration modes used in the study are referred to as the Chronic Mode, LATITUDE Mode, Hospitalization Mode, and Discharge Mode. In the Chronic Mode, SRD-1 sensor data are allocated approximately 8 weeks of storage memory and are saved using the programmer at regular intervals. In the LATITUDE Mode, SRD-1 data are stored for approximately 3 weeks, and automatically and remotely downloaded from the subject’s home every week for subjects who are enrolled in LATITUDE. The Hospitalization Mode is used if it is known that the patient is hospitalized for worsening HF at an investigational center. In the Hospitalization Mode, SRD-1 sensor data are collected at high sampling rates for approximately 1 week and saved to disk periodically until discharge (up to a maximum of 28 days). At discharge, the SRD-1 is reconfigured to the Discharge Mode, and SRD-1 data are collected for 2 weeks until the post-discharge follow-up visit. It is anticipated the frequency of data collection will not need to be very high. For most analyses, the chronic mode (lowest data frequency) will provide enough data. Higher rates of data collection will be used in exploratory analyses.

The SRD-1 PG provides the same therapy and diagnostic features as the COGNIS except for the following modifications: 1) short delay (40 s) in rate-responsive pacing due to heart sound data collection; 2) removal of Smart Delay™ AV-optimization; 3) removal of some VF induction methods; 4) reduced electrogram storage; 5) removal of the diagnostic features of patient-triggered monitoring and autonomic balance monitoring; and 6) a reduction in accuracy of the activity-log diagnostic due to heart sounds data collection. Owing to the high sampling and data collection rate utilized in the study for analysis purposes, participation in the study may impact overall device longevity by up to 6 months out of a projected total device longevity of 7.7 years for the COGNIS CRT-D devices used in the trial. All other modifications are temporary and will be restored at the end of the study. If a study subject develops a need for
any of the removed device functionality, withdrawal from the study and reconversion to COGNIS will restore original device functionality. Additionally, an automatic time-out feature will terminate research data collection 1 year after device configuration to prevent unnecessary extra battery utilization if a subject is lost to follow-up. Each study investigator will monitor the occurrence of adverse events and adverse device effects for each enrolled subject. All documented adverse events will be reviewed and reported to comply with applicable regulations and vigilance requirements. An independent Data Safety and Monitoring Board will periodically review study progress and adverse events to provide additional safety oversight. The SRD-1 software will not be able to monitor patient posture. Accordingly the study also collects data from an external posture monitoring device (PMD). The PMD is a single-use investigational device that contains a three-axis accelerometer for sensing body orientation at the pectoral region of the thorax. The PMD continuously samples subject posture and activity data and stores it for up to 14 days. For subjects with a pectoral PG implant, the PMD must be attached contralateral to the implanted device. The device is affixed using adhesive foam over an adhesive semipermeable dressing (e.g. Tegaderm®, 3M Nexcare, St. Paul, MN) applied on the skin. Posture data collection using the PMD is recommended in the first 30 patients at the beginning of the study, and optionally in all patients during HF hospitalization events and during the post-discharge period following an HF hospitalization.

**Follow-up**

Follow-up visits are required to save SRD-1 data to disks and record subject clinical information. The majority of sensor data is collected either at Chronic follow-up visits or remotely via LATITUDE. Clinical information recorded at each follow-up includes vital signs, cardiac disease history, comorbidities, HF assessment, and changes in HF medications. The time interval between follow-up visits varies during the course of the study. The follow-up schedule for the study is summarized below.

- **Enrollment and conversion:** At enrollment, subject baseline data including demographics, device information, cardiac disease history, and comorbidities are collected. Following enrollment the subject’s device is converted to an SRD-1 within 44 days but no earlier than 30 days post implant. Upon enrollment and device conversion, subjects will be given a diary to record daily weight and diuretic changes, and complete a weekly self-assessment score reflecting overall HF symptom burden (including shortness of breath, fatigue, and swelling).
- **Two-week follow-up:** In the first 30 enrolled patients a 2-week follow-up visit is used to collect SRD-1 data and, if applicable, PMD data.
- **Chronic follow-up:** Subjects not enrolled in LATITUDE and whose devices are configured to the Chronic Mode have follow-up visits every 6–8 weeks.
- **LATITUDE follow-up:** Subjects enrolled in LATITUDE have their SRD-1 devices configured to the LATITUDE mode and have follow-up visits every 12 weeks.
- **Post-discharge follow-up:** At discharge where the SRD-1 is reconfigured to the Discharge Mode, a post-discharge follow-up visit is required within 2 weeks following discharge.
- **Re-conversion follow-up:** This visit must be conducted no later than 12 months after COGNIS to SRD-1 conversion. At this visit the SRD-1 device is converted back to a COGNIS device.
- **Device check follow-up:** This visit is used for device evaluation and is conducted 30–44 days after the SRD-1 is reconverted to a COGNIS. This follow-up visit ends the subject’s participation in the study.

During the study, investigators have access to the device information currently available in the market released CRT-D device; however, both patients and investigators are blinded to the investigational sensor data. Clinical management of HF remains standard-of-care based on typical practice and is not impacted by the study protocol.

**Events**

An HF event is defined as either of the following:

- **HF Hospitalization,** where the subject is admitted to the hospital with signs/symptoms of congestive heart failure and receives unscheduled augmented HF therapy with oral or intravenous medications, ultra-filtration therapy, or other parenteral therapy (formal hospital admission is defined as an admission involving a calendar date change); or
- **HF Outpatient Visit,** where subject has signs/symptoms of congestive heart failure, and receives unscheduled intravenous (IV) decongestive therapy (e.g. IV diuretics, IV inotropes, IV vasoactive drugs) that does not involve formal inpatient hospital admission, regardless of the setting (e.g. an emergency room setting, in the physician’s office, etc.).

The above-defined HF events are the primary data that will be used for algorithm development; however, sensor measurements will also be investigated in association with changes in HF medications prescribed by the clinician, and non-HF related hospitalizations. Non-HF hospitalizations may occur due to cardiac causes other than HF (such as myocardial infarction, arrhythmia, complications of HF medications, etc.), or non-cardiac causes (such as pulmonary, gastrointestinal, renal, etc.). For the purposes of capturing a broader set of clinical events, Reviewable Clinical Events (RCVEs) are defined as all-cause hospitalizations, or outpatient visits with augmented oral HF medications or any IV therapy. At each study visit, information about RVCEs is captured in case report forms, and complete medical records are obtained. All RVCEs and deaths are adjudicated by an independent clinical events committee (CEC) composed of cardiologists with device and heart failure expertise. A CEC charter approved by CEC members is used to standardize the event source documentation, adjudication methodology, and documentation of results.

**Data analysis**

Data collected from SRD-1 sensors will be used in combination with clinical baseline and event data to
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develop HF algorithms. Initial analyses will focus on the performance of each individual sensor parameter to predict an HF event. Each sensor may be broken down into more than one parameter. For example, respiratory data may be divided into respiratory rate, relative tidal volume, and relative minute ventilation. Respiratory rate may be further divided into minimal, maximal, mean, and median respiratory rate. Once the single sensor parameter assessments are completed, work will commence on combining several sensor parameters to develop a multisensor algorithm. The choice of sensor parameter will be driven by predictive ability of the individual parameter and the value to complement the predictive ability of the algorithm when combined with other sensor parameters. In general, each parameter in the multisensor algorithm will provide unique insight into the physiologic changes that occur during an HF exacerbation.

The number of HF events used historically for algorithm development has varied across studies. Since this is a feasibility trial for the purpose of sensor characterization and algorithm development, and the methodologies used to combine sensor data may be modified by initial findings, no formal methods were used to predetermine endpoints or calculate sample size. Based on prior studies such as DECODE,12 where 135 HF events were used to develop and evaluate an algorithm, and the comparatively closer association expected between SRD-1 sensors and HF pathophysiology, we estimate that approximately 100 usable HF events will be needed for signal analysis and algorithm development, which will include interim division into development and test sets to limit data overfitting. Broad patient eligibility criteria are used so that the study sample represents the heterogeneity known to exist within the CRT-D HF patient population arising from various factors such as disease etiology, demographic differences, and comorbidities. The study sample size has not been independently powered for analysis of individual subgroups. Estimating an HF event rate of 0.2 events/patient-year, a 25% subject attrition due to death or withdrawal, and a subject follow-up of 1 year (with SRD-1 data), a total of 900 subjects who are successfully enrolled with device conversion to SRD-1 are required to obtain 135 HF events. Assuming that 25% of the events are unusable (due to either gaps in sensor data collection, or events that occur in proximity), 100 events with sufficient data will be available.

Discussion

MultiSENSE is designed to collect chronic ambulatory sensor data from implanted sensors associated with the signs and symptoms of worsening HF along with detailed data about patient events and medication changes. These data are expected to enable a closer evaluation of physiologic changes leading up to HF events than was previously possible. The chronic behavior of measurements such as respiration, intrathoracic impedance, heart sounds, and physiological response to activity may provide new insights into the progression of worsening HF and enable development of algorithms which can be incorporated into future devices and can improve patient management through earlier intervention. The hardware needed for these sensors is already included in many implantable electronic devices, eliminating the need to implant additional devices. Since the morbidity and costs of HF hospitalization are major clinical concerns, the ability to clinically intervene in worsening HF at an early stage could lead to a reduction in morbidity and possibly a reduction in the increased mortality associated with HF hospitalization, and could facilitate more cost efficient care. The concept of using multiple sensors is modeled after the typical clinical evaluation of patients, where multiple clinical variables including signs, symptoms and laboratory findings are combined to establish a diagnosis. In the case of an implantable device, monitoring can occur continuously in any setting, and the calculation of the risk of an impending event can be performed by the device without any inconvenience to the patient. Since many HF patients already require an implantable cardiac device, these patients would not need additional hardware or leads that may add further complexity to their care.

There are several novel aspects to the study design. First, the study focuses on combining the information gained from several different types of signals, each one of which may provide important information alone. Therefore, we anticipate that combining the signals will enhance the overall performance of the final algorithm. The device also collects sensor data at several different sampling rates, to allow for more intensive data collection and analysis during HF hospitalization and recovery time periods. Additionally, the HF detection method under study utilizes hardware already available in existing patient therapy devices without the need for additional equipment or invasive procedures.

The advent of remote patient management further increases the utility of device diagnostics, enabling a view into patient status outside of scheduled clinic visits. Remote follow-up of implantable cardioverter-defibrillator (ICD) and CRT-D device data is associated with a 50% relative reduction in the risk of death.21 Of the remotely monitored CRT-D cohort, the subset of subjects additionally transmitting weight and blood pressure data had the lowest mortality risk. The addition of diagnostic technology with increased specificity to detect worsening HF status could further enhance the utility and benefit of remote patient monitoring.

To date, the performance of sensors and strategies evaluated to provide early indications of worsening HF has been limited. Chaudhry et al.11 demonstrated that while increased body weight was associated with HF hospitalization a weight gain of more than 2 pounds prior to hospitalization occurred in only 46% of patients, and 23% of patients who did not require hospitalization experienced a similar weight gain. More recent studies on disease management programs based on weight monitoring, which depend not only on the sensors used but also
on patient compliance and intervention, have not had significant impact on outcomes including hospitalizations. While implanted hemodynamic monitoring has shown promise, it requires dedicated implants or leads. Sensors available in implanted devices such as thoracic impedance have been shown to have value for patient monitoring. However, the detection performance of this individual sensor in prospective studies has been lower than initially reported (SENSE-HF: sensitivity of 20.7% and PPV of 4.7%17,26). In a recent study by Auricchio et al.29 evaluating minute ventilation and physical activity also showed lower than expected performance (sensitivity of 34% and FPR of 2.4 per patient-year).

While single sensor performance has been less than desirable, several studies have demonstrated the benefits of using multiple sensor diagnostics in HF patient management. The PARTNERS-HF study evaluated the utility of combining existing device diagnostics with impedance and showed that patients with a positive combined HF device diagnostic score had a 5.5-fold increase in risk for HF hospitalization within the next 30 days. In another retrospective analysis on data from four studies including PARTNERS-HF, Whellan et al. demonstrated that diagnostic criteria based on device diagnostics evaluated 7 days after discharge identified patients at higher risk of 30-day readmission. In both studies, the performance of multiple device diagnostics was superior to that of impedance alone. The DECODE study developed and tested an algorithm based on heart rate, heart rate variability, activity, lead impedance, weight, and patient symptoms in CRT-D patients. Since the device diagnostics used were not specifically designed for acute HF monitoring, algorithm performance was suboptimal (sensitivity of 35% with a FPR of 2 per patient-year). However, the authors demonstrated that combining multiple measures improved performance for identifying worsening HF. Similarly, the MUSIC study demonstrated that an external multisensor monitoring system and a multiparameter algorithm (based on impedance, breath index, and patient baseline information) had superior performance (sensitivity of 65% with an FPR of 0.7 per patient-year) than impedance alone (sensitivity of 8% with an FPR of 9.4 per patient-year). The sensors being evaluated in the MultiSENSE study were specifically designed to measure physiological variables associated with signs and symptoms of worsening HF and are thus expected to improve performance. With all of the capability existing within the implantable electronic device, the entire process is invisible to patients, thus compliance with monitoring will not be a concern. The study will have a few limitations. The PMD data will only be capable of providing feasibility for the parameter individually, and will require future studies to be incorporated into the multiparameter algorithm. The number of sites needed and the multinational nature of the study will introduce some variability into what constitutes an HF event. To provide a uniform evaluation of an HF event, a rigid process of event adjudication was utilized. Finally, the actual event rate and the attrition rate may impact the number of events observed in the study, thus affect the representativeness of HF events in the general HF population.

Conclusion

The MultiSENSE study will collect data from multiple sensors contained within an implantable electronic device while monitoring patients’ HF status in order to develop future device features which facilitate the management of worsening HF at an early stage. The concept of combining multiple sensors to more accurately identify worsening HF is modeled after clinical practice where data are combined by the clinician to make an assessment of a patient’s condition. It is anticipated that an effective algorithm for early identification of worsening HF will lead to better treatment of the HF condition and fewer HF related hospitalizations, and may lower overall cost of care.

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