

# Reducing Events in Patients with Chronic Heart Failure (REDUCE<sub>hf</sub>) Study Design: Continuous Hemodynamic Monitoring with an Implantable Defibrillator

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## Summary

**Background:** The use of implantable cardioverter defibrillators (ICDs) has been proven effective in the prevention of sudden cardiac death (SCD) and constitutes standard of care in appropriate populations. Combining a pressure sensing system with ICD therapy represents the first attempt to provide continuous hemodynamic monitoring using a device previously designed exclusively for SCD protection.

**Methods:** REDUCE<sub>hf</sub> is a prospective, multicenter, randomized, single-blind, parallel-controlled trial designed to assess the safety of the Chronicle ICD system (single chamber ICD with a hemodynamic monitoring system) and the effectiveness of a management strategy guided by intracardiac pressure information among ICD-indicated New York Heart Association (NYHA) Class II or III heart failure (HF) patients. Those successfully implanted with a Chronicle ICD will be randomized to the Chronicle group or Control group. All patients

will receive optimal medical therapy, but the hemodynamic information from the device will be used to guide patient management only in the Chronicle group. Primary endpoints include freedom from system-related complications and relative risk reduction of one or more HF-related events (hospitalizations, and emergency department and urgent care visits requiring intravenous therapy for HF). Approximately 850 patients will be enrolled in at least 75 centers in the United States to accrue the 419 events needed to test the primary effectiveness endpoint. Enrollment began in April 2006, and is expected to end during 2009.

**Conclusion:** REDUCE<sub>hf</sub> will assess the safety of the Chronicle ICD system and the effectiveness of a patient management strategy based on remote access to continuous intracardiac pressures in reducing HF-related events.

**Key words:** heart failure, disease management, ambulatory monitoring, hemodynamics, hospitalization, implantable cardioverter defibrillators

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## Introduction

### Background

Despite marked reduction in heart failure outpatient morbidity and mortality achieved by drug and device therapies over the past 10 years, outcomes of patients hospitalized for heart failure remain unacceptably high.<sup>1</sup> Admissions due to worsening congestive heart failure

are associated with high mortality (4% in-hospital), predict subsequent morbidity (50% rehospitalization within 6 months) and further promote myocardial damage and adverse remodeling.<sup>1-3</sup> In addition to the direct deleterious effects of the congestive state, exposure to high-dose diuretics and other medications (e.g. inotropes) during the hospital stay may further worsen cardiac and renal function over time.<sup>3</sup> Therefore, a management strategy aiming to reduce hospitalizations may be effective in both slowing disease progression and decreasing the overall burden of heart failure.

Volume overload and congestion are the hallmarks of most hospital admissions for worsening heart failure.<sup>4</sup> Therefore, maintaining fluid volume status within an optimal range—while avoiding both volume overload and depletion—should be the ultimate goal of any ambulatory heart failure management strategy. However, in current clinical practice, serial assessments rely on insensitive and indirect methods to assess volume, such as history and physical examination, coupled with patient-reported changes in daily weights. Even in the hands of trained specialists, physical examination correlates poorly with filling pressures or volume and can only be performed intermittently during direct patient encounters.<sup>5,6</sup> Similarly, weight gain is a very specific yet insensitive measure of impending decompensated heart failure, that is, its presence almost always denotes clinical deterioration, but the vast majority of clinical events are not preceded by such weight gain.<sup>7</sup> Therefore, an ideal tool to monitor heart failure patients would be one that continuously records filling pressures as a direct measure of the parameter other assessment methods only attempt to estimate fluid volume status.

### **Sudden Cardiac Death and Implantable Cardioverter Defibrillators Therapy**

The use of implantable cardioverter defibrillators (ICD) for the primary or secondary prevention of sudden cardiac death (SCD) has been proven to be effective and now represents standard of care in appropriate populations.<sup>8-12</sup> This important therapy has great clinical utility, since SCD is the leading cause of cardiovascular mortality in industrialized nations, and the risk of lethal tachyarrhythmias increases as left ventricular function declines.<sup>13,14</sup> Hopes of survival from potentially lethal arrhythmias depend on rapid electrical intervention, which is best achieved by an ICD. However, in a given patient, the benefit of ICD therapy in prolonging life manifests itself only when a treatable electrical episode is sensed by the device.

### **Implantable Devices and Continuous Patient Monitoring**

Since ICD-indicated patients often exhibit signs and symptoms of underlying congestive heart failure,<sup>8-12</sup>

several attempts have been made to harness physiologic information acquired by implanted devices to enhance the day-to-day management of this chronic disease.<sup>15-18</sup>

One of the first attempts to utilize the monitoring capabilities of an implanted therapeutic device was the reporting of continuously measured heart rate variability (HRV) in patients with heart failure.<sup>16</sup> As measured from an implanted electrical device, HRV declined significantly in association with the development of volume overload and congestion, suggesting vagal withdrawal and sympathetic activation as patients decompensated to the point of hospital admission.<sup>17</sup> Significant physiologic alterations in cardiac autonomic control were noted several weeks before patients actually sought medical attention, suggesting that the progression to congestive decompensation begins long before patients present with overt signs or symptoms of worsening heart failure. In addition to potentially serving as an early warning mechanism, device-enabled physiologic monitoring offers the distinct advantages of continuous data acquisition in the patient's own environment with the opportunity for remote data access using secure Internet-based information systems. Ambulatory hemodynamic monitoring should prove superior even to multidisciplinary heart failure treatment programs that specialize in frequent clinical encounters to avoid clinical decompensation.

No prospective trials are yet available to understand how chronic device-based monitoring of arrhythmias, HRV,<sup>18</sup> or intrathoracic impedance<sup>15</sup> may improve heart failure outcomes. However, the addition of monitoring capabilities to implantable devices marks the beginning of a new patient management era that includes the use of remotely acquired device-based clinical data in the management of chronic disease.

### **Chronicle Implantable Hemodynamic Monitoring Systems**

An implantable continuous hemodynamic monitoring (ICHM) system (Chronicle, Medtronic, Inc., Minneapolis, Minn., USA) was developed to continuously measure intracardiac pressures. This ICHM has been shown to accurately represent intracardiac pressures over time when compared with Swan-Ganz catheterization over a variety of physiological conditions.<sup>19,20</sup> In addition, preliminary data suggested that a stand-alone chronically implanted monitor for patients with heart failure would provide clinical value by reducing heart failure-related hospitalizations.<sup>21</sup> A recent prospective randomized clinical trial, the Chronicle Implantable Hemodynamic Monitor Offers Management to Patients with Advanced Heart Failure (COMPASS-HF) study, evaluated the clinical utility of a patient management strategy guided by continuous intracardiac pressures, as measured by the Chronicle ICHM. This trial was the first to evaluate the clinical benefit of an implantable device

solely dedicated to monitoring without delivering direct therapy. The COMPASS-HF trial met its safety objective in that the implementation of this patient management strategy revealed no evidence of fluid imbalance or electrolyte complication. These same strategies were associated with a nonstatistically significant reduction in heart failure events among patients with New York Heart Association (NYHA) Class III or IV heart failure who previously required hospital admission or intravenous therapy for worsening heart failure.<sup>22</sup> Importantly, however, COMPASS-HF demonstrated the sustained increase in intracardiac pressures in the weeks leading to clinical intervention for hypervolemia and the subsequent drop in pressure following treatment. These results further indicate the importance of the physiologic premise underlying continuous hemodynamic monitoring, whereby early detection of sustained increases in pressure may provide an opportunity for earlier intervention that would change the physiologic course of a developing decompensation and potentially avoid the impending clinical deterioration and hospital admission.

The next logical step in technology development was to combine the hemodynamic monitoring capabilities of the ICHM with an implantable therapy-delivering device, such as an ICD for SCD protection. We report here the design of the REDucing Decompensation events Utilizing intraCardiac prEssures in patients with chronic Heart Failure (REDUCE<sub>hf</sub>) trial, which is designed to evaluate the safety of the combination device, Chronicle ICD, and the effectiveness of a Chronicle-guided patient management strategy among patients who are indicated for ICD therapy.

## Methods

### Study Design

REDUCE<sub>hf</sub> is a prospective, randomized, single-blind, parallel-controlled trial. Patients successfully implanted with a Chronicle ICD system will be randomized to either a group that will continue to receive standard heart failure care with no access to ambulatory intracardiac pressure information (Control), or a group that will continue to receive standard heart failure care in addition to an ICHM-guided patient management strategy (Chronicle). Patients will not be aware of their group assignment during the 12 months of randomized follow-up, and both groups will be required to transmit device information using the Home Monitor at least weekly. Beyond the randomized follow-up period, intracardiac pressure information will be made available for the management of patients in both groups. Patients will then be followed every 6 months until FDA approval or study completion (Fig. 1). Approximately 850 patients will be enrolled in at least 75 centers in the United States. The study protocol must be approved by the institutional review board of each participating center, and all patients will provide written informed consent.

### Patients

Patients will be eligible for enrollment in the study if they are at least 18 years old; have NYHA class II or III heart failure; have a clinically accepted indication for ICD therapy; receive optimized standard medical therapy (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a beta-blocker; all medications as tolerated) for at least 3 months prior to baseline evaluation; and have had at least one heart failure-related event within the previous 12 months (Table 1).

Patients will be excluded from the study if they have an existing implantable cardiac rhythm management device (except a single-chamber ICD being considered for upgrade to a Chronicle ICD); an indication for atrial pacing and/or cardiac resynchronization therapy; severe chronic obstructive pulmonary or severe restrictive airway disease; primary pulmonary artery hypertension; known atrial or ventricular septal defects; tricuspid or pulmonary stenosis; mechanical or bioprosthetic right heart valves; a severe, noncardiac condition limiting 12-month survival; estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> (using the Modification of Diet in Renal Disease equation)<sup>23</sup> or on chronic renal dialysis; are likely to undergo cardiac transplantation within 12 months of implant; are receiving continuous or intermittent intravenous doses of vasoactive agents and/or positive inotropic therapy; or females of child-bearing age not using reliable contraceptive measures (Table 2).

### Study Procedures

Intracardiac pressures derived from the hemodynamic monitoring system will form the basis of a patient management strategy recently implemented as part of the COMPASS-HF study.<sup>22</sup> The strategy first calls for the determination of a patient-specific filling pressure range consistent with the best balance between signs and symptoms of congestion and evidence of low cardiac output. This pressure range is then regarded as representing an optimal volume state—or optivolemia—and constitutes the patient's individualized baseline. During the randomized follow-up period, clinicians will review the hemodynamic data of patients in the Chronicle group at least weekly. Following each review of the pressure information, patients will be classified as being in one of three predefined volume states: optivolemic, hypovolemic, or hypervolemic (Table 3). Each volume state is associated with appropriate treatment recommendations adapted from the 2005 ACC/AHA guidelines for the management of chronic heart failure.<sup>12</sup> The goal of intervention, if initiated, is to restore optivolemia.

Pressure information derived from the system will be reviewed and acted upon by clinicians experienced in the management of heart failure. Electrophysiologic and system integrity related data will be reviewed by implanting

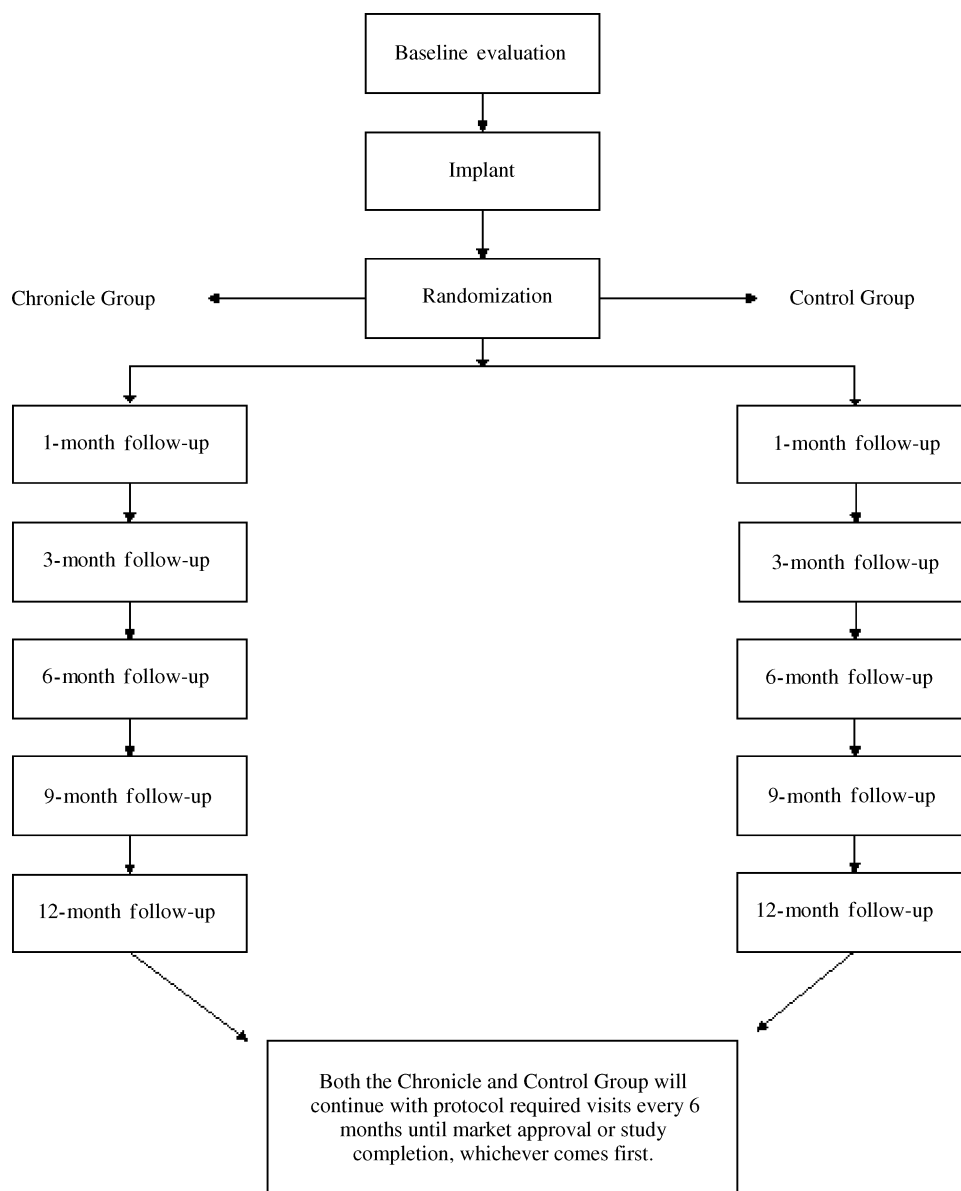


FIG. 1 Patient enrollment and follow-up scheme.

physicians and device clinics for evaluation of battery life, lead performance, and detection or treatment of potentially lethal tachyarrhythmias.

An independent data monitoring committee and an independent adverse events adjudication committee have been formed.

### Blinding

This study will require that clinicians interact with patient-specific hemodynamic information (Chronicle group) and implement appropriate individual treatment plans. Therefore, unlike their patients, clinicians will not be blinded to the randomization assignment, consistent with a single-blinded study design.

All randomized patients will undergo a Chronicle ICD implant, and active measures will be taken to preserve their blinding. First, to maintain consistency between the groups, all patients will be asked to transmit their ICHM information at least weekly during the randomized follow-up period. Second, to ensure that nonblinded caregivers will not inadvertently disclose the patient's randomization assignment, standardized clinician communication scripts will be employed. These scripts will include questions related to standard management of heart failure (e.g. shortness of breath, weight gain), but will not include any reference to intracardiac pressures. Third, heart failure providers will not interrogate the device in the office in order to prevent inadvertent unblinding. Lastly, because clinician interaction with

TABLE 1 Inclusion criteria

- 
- Written informed consent and authorization to use and disclose health information
  - 18 years of age or older
  - Clinically accepted indication for ICD therapy
  - New York Heart Association Class II or Class III at baseline
  - Diagnosed with heart failure at least 3 months prior to baseline evaluation
  - Appropriate medical therapy for heart failure (such as diuretic, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and beta-blocker) for at least 3 months prior to the baseline evaluation. Subject has been on stable medications maximized to the subject's tolerance of ACE or ARB and beta-blockers as determined by the study investigator for at least 30 days prior to baseline evaluation. Stable is defined as no more than a 100% increase or a 50% decrease in dose. If a subject is intolerant of ACE, ARB or beta-blockers documented evidence must be available.
  - At least one heart failure-related hospitalization or at least one heart failure-related emergency department or urgent care visit necessitating heart failure-related intravenous therapy (e.g. diuretic administration) within 12 months prior to the baseline evaluation
  - Willing and able to comply with the protocol
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TABLE 2 Exclusion criteria

- 
- Existing or prior ventricular assist device, pacemaker, dual chamber ICD, CRT, CRT-D, Chronicle system or abandoned pacing or defibrillator lead(s)
  - Existing single chamber ICD without a high voltage, true bipolar right ventricular defibrillation lead
  - NYHA Class IV or Stage D refractory heart failure
  - Abdominal device placement
  - Unstable angina requiring hospitalization, acute myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention within 40 days prior to baseline evaluation
  - Severe chronic obstructive pulmonary disease (COPD) or severe restrictive airway disease as defined by the GOLD classification of COPD
  - Continuous or scheduled intermittent intravenous administration of vasoactive compounds and/or positive inotropic therapy
  - Known atrial or ventricular septal defects
  - Mechanical or bioprosthetic right heart valve
  - Primary pulmonary arterial hypertension
  - Indication for atrial pacing (sinus chronotropic incompetence)
  - Indication for CRT
  - History of right-sided endocarditis due to intravenous substance abuse
  - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m<sup>2</sup> using the Modification of Diet in Renal Disease (MDRD) equation
  - Chronic renal dialysis
  - Expected cardiac transplantation within 12 months from Chronicle ICD implant, or expected to remain hospitalized until transplantation
  - Severe noncardiac condition limiting 12-month survival
  - Enrollment in concurrent studies that may confound the results of this trial
  - Women who are pregnant or with child bearing potential not on a reliable form of birth control
- 

*Abbreviations:* NYHA = New York Heart Association, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillators.

ICHM information is expected to result in an increased frequency of calls to the Chronicle group patients (e.g. changes in pressure that might warrant a medication change), proactive surveillance calls to the Control group will be initiated to balance the number of communications between the two groups.

### Endpoints

The REDUCE<sub>hf</sub> trial will have two primary endpoints: (i) a safety endpoint that will assess the freedom from complications related to the implanted system, and (ii) an effectiveness endpoint that will assess the utility of

an ICHM-guided patient management strategy in reducing the risk of one or more heart failure-related events, including hospitalizations, and emergency department and urgent care visits requiring intravenous therapy for heart failure.

Several secondary endpoints will be examined, with prespecified hypotheses that will be tested in a hierarchical fashion: cumulative days in hospital for heart failure, risk of all cardiovascular events, risk of all-cause mortality or heart failure-related hospitalization, the composite response score,<sup>24</sup> and risk of all-cause events.

In addition, intracardiac pressure data prior to and during potentially lethal ventricular arrhythmias will

TABLE 3 Volume status definitions

	Hypervolemia	Optivolemia	Hypovolemia
Symptoms	Congestive symptoms (wet)	Minimal congestive symptoms and minimal evidence of poor perfusion	Poor perfusion with no symptoms of congestion (dry)
Individual Pressure Parameters	Above optivolemic range	tRVSP: 25–40 mmHg <sup>a</sup> RVDP: 4–10 mmHg <sup>a</sup> ePAD: 8–18 mmHg <sup>a</sup>	Below optivolemic range
Nightly minimum trends (lowest pressure between midnight and 4:00 A.M. with no activity)	Elevation in trend data above optivolemic range	Inside optivolemic range	Decrease in trend data below optivolemic range
1-week, 1-month, 1-year trends (Continuous measurements)	Elevation in trend data	Stable trend data	Decrease in trend data

<sup>a</sup> Recommended starting range, set during the first weeks postimplant.

Abbreviations: RVSP = right ventricular systolic pressure, RVDP = right ventricular diastolic pressure, ePAD = estimated pulmonary artery diastolic.

be examined to characterize the temporal relationship between hemodynamic status and the onset of arrhythmias detected and treated by the device.

### Statistical Analysis

For the primary effectiveness endpoint, for the purpose of sample size calculations, we assumed that the Chronicle group will demonstrate a 30% reduction in the relative risk of one or more heart failure-related events (hospitalizations, emergency department and urgent clinic visits requiring intravenous therapy) compared to the Control group. We determined that 419 events will be needed to test the hypothesized difference in the relative risk between the two groups with 80% power ( $\alpha = 0.05$ ). This assumes four planned analyses at equal increments of heart failure-related events, which will be reviewed by the Data Monitoring Committee. Stopping boundaries have been predefined based on O'Brien and Fleming shape parameters. On the basis of a hypothesized event rate of 0.85 per 12 patient-months of follow-up in the Control group, approximately 850 randomized patients will be required to accrue the 419 heart failure-related events needed to evaluate the primary effectiveness endpoint of the study. The primary effectiveness endpoint will be analyzed using the Anderson-Gill methodology, a generalization of the Cox proportional hazards regression model to accommodate for multiple events in the same patient.

For the primary safety endpoint, we hypothesize that at 6 months, the freedom from system-related complications will be greater than 80%. A system-related complication will be defined as any adverse event related to the system (ICD and both leads) that will be treated with invasive means; results in the death or serious injury of a

patient; results in the explant of any system component; or causes permanent loss of significant function of the system. The freedom from system-related complications will be analyzed using the Kaplan-Meier methodology. The sample size required to test the primary effectiveness objective will be more than adequate to test the primary safety objective.

### Device Description

The Chronicle ICD (Model 7286, Medtronic, Inc.) system consists of the following: (i) a single-chamber ICD with a pacing- sensing- defibrillation lead positioned in the right ventricular apex, and (ii) an additional transvenous lead (Model 4328A, Medtronic, Inc.) positioned in the right ventricular outflow tract that has a sensor incorporated near its tip to measure intracardiac pressure. The sensor was previously validated and found to be highly accurate.<sup>19–21</sup>

The system is capable of monitoring and storing heart rate, body temperature, patient activity, right ventricular systolic and diastolic pressure, maximal positive and negative rate of change in right ventricular pressure (dP/dt), right ventricular pre-ejection and systolic time intervals, and estimated pulmonary arterial diastolic pressure (ePAD).<sup>25</sup> The ePAD is defined as the right ventricular pressure at the time of pulmonary valve opening, which occurs at the time of maximal dP/dt.<sup>25–27</sup> A strong correlation ( $r = 0.84$ ) has been shown to exist between ePAD and actual pulmonary artery pressures measured under a variety of physiologic conditions.<sup>19,25,27,28</sup>

Since the system records absolute pressure, which includes both physiologic and ambient pressures, all pressure data are corrected for barometric pressure

using a small external pressure reference device (Model 2956HF, Medtronic, Inc.) carried by the patient (Fig. 2).

### Hemodynamic Data Flow

The hemodynamic monitoring component of the system measures pressure on a beat-to-beat basis, but commits to memory one data point every preset time interval, most often set to approximately 8.5 min. Each data point reflects the median as well as the 6th and 94th percentiles of all measurements taken within the respective time interval. All patients are instructed to transmit the information from the device at least weekly using a home monitor that interrogates the device via a hand-held radio frequency wand and transmits the data through a standard phone line to a secure server (the patient is not required to have Internet access). The clinician can then access the data on the Chronicle Web site using a conventional Internet browser. The Web site automatically concatenates new data received from the device with data from previous transmissions and provides visual representation of the data in the form of trends over time.

### REDUCE<sub>hf</sub> versus COMPASS-HF

COMPASS-HF was the first-of-a-kind trial that tested the utility of a patient management strategy based on remote access to continuous intracardiac pressures in reducing the rate of heart failure-related events (as defined above) in 274 NYHA Class III and IV heart

failure patients implanted with a stand-alone ICHM system. The study reported a 21% nonstatistically significant reduction in event rates between the Chronicle and Control group, but a retrospective Cox regression analysis revealed a 36% reduction in the relative risk of a heart failure-related hospitalization.

Several observations from the COMPASS-HF trial were used to guide the design of the REDUCE<sub>hf</sub> trial. First, the actual event rate in the Control patients of COMPASS-HF was 29% lower than expected (0.85 vs. 1.2 heart failure-related events per 6 patient-months of follow-up), likely because the frequent calls made to Control patients as part of the rigorous blinding policy constituted an “active intervention” rather than a true “standard-of-care” arm.<sup>22</sup> REDUCE<sub>hf</sub> is designed to be “event-driven”, i.e. the power calculations are based on the number of events needed to detect the hypothesized difference between the groups and are not based exclusively on follow-up time or number of enrolled patients. The effectiveness endpoint of REDUCE<sub>hf</sub> will be expressed in terms of risk of one or more heart failure events rather than rate of heart failure-related events, as was done in COMPASS-HF. Finally, the patient management strategy evaluated in both studies requires an initial period of customization to individual patients. Since this process may take several weeks, it was deemed appropriate to extend the randomized follow-up period from 6 month in COMPASS-HF to 12 months in REDUCE<sub>hf</sub>. Table 4 provides a detailed comparison between the COMPASS-HF and REDUCE<sub>hf</sub> trials.



FIG. 2 The Chronicle ICD system includes the implantable device (A), a home monitor (B) that enables remote interrogation of the device and data transmission over standard telephone lines to a secure Web site. Absolute intracardiac pressure measured by the device are adjusted for barometric pressure captured by a time-synched external pressure reference (C) carried by the patient. The device can also be interrogated using a standard programmer (D).

TABLE 4 Comparison between REDUCE<sub>hf</sub> and COMPASS-HF trial designs

	COMPASS-HF	REDUCE <sub>hf</sub>
Implanted device	Chronicle ICHM (stand-alone, single lead, implantable continuous hemodynamic monitoring system)	Chronicle ICD (a single chamber ICD combined with a continuous hemodynamic monitoring system)
Safety endpoint(s)	<ul style="list-style-type: none"> <li>Freedom from system-related complications at 6 months <math>\geq 80\%</math></li> <li>Freedom from pressure sensor failure at 6 months <math>\geq 90\%</math></li> </ul> Analytical method: Kaplan–Meier survival	Freedom from system-related complications at 6 months $>80\%$ Analytical method: Kaplan–Meier survival
Effectiveness endpoint	Reduction in the rate of heart failure events per 6 months Assumed reduction (for sample size calculations): 30% Analytical method: negative binomial regression	Reduction in the relative risk of one or more heart failure events Assumed reduction (for sample size calculations): 30% Analytical method: Anderson–Gill method
Patients	NYHA Class III or IV with heart failure event in previous 6 months	NYHA Class II or III with heart failure event in previous 12 months
Sample size	1,354 patient-months of randomized follow-up	419 heart failure events
Randomized follow-up	6 months	12 months
Randomized patients	274 (actual)	850 (anticipated)

Abbreviations: ICHM = implantable continuous hemodynamic monitor, ICD = implantable cardioverter-defibrillator, NYHA = New York Heart Association.

## Conclusions

SCD remains a leading cause of mortality in industrialized nations, claiming 300,000–600,000 lives per year in the United States alone.<sup>13</sup> The use of ICD therapy has been proven effective in reducing mortality and constitutes the standard of care in appropriate populations.<sup>12</sup>

Advancement in ICD technology to include physiologic monitoring systems may be an important step toward increasing the value of therapy delivering devices in larger populations with heterogeneous risk. Combining pressure sensing systems with ICD therapy represents the first attempt to provide continuous hemodynamic monitoring using a device previously designed exclusively for SCD protection. This added capability should enhance the clinical value of an ICD by enabling superior heart failure management through the direct measurement of dynamic, clinically meaningful physiologic parameters.

The REDUCE<sub>hf</sub> trial will enroll approximately 850 patients with NYHA Class II and III heart failure who meet a current indication for ICD therapy to reduce the risk of SCD. The first patient was enrolled in April, 2006, and enrollment is expected to be completed during 2009. The trial will examine the safety of the Chronicle ICD system and whether a heart failure management strategy based on ambulatory intracardiac pressures is effective in reducing heart failure events associated with heart failure.

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