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November 03, 2022

Ms. Tamara Syrek-Jensen, J.D.
Director, Coverage & Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244

Via email at Tamara.SyrekJensen@cms.hhs.gov

FORMAL REQUEST FOR A NATIONAL COVERAGE DETERMINATION (NCD) FOR REMOTE IMPLANTABLE HEMODYNAMIC MONITORING FOR HEART FAILURE

Dear Ms. Syrek-Jensen,

Enclosed please find Abbott's formal request for a National Coverage Determination (NCD) for remote implantable hemodynamic monitoring for heart failure (e.g., CardioMEMS™ Heart Failure System). Abbott believes that a national coverage policy for remote implantable hemodynamic monitoring with the CardioMEMS™ Heart Failure (HF) System will ensure long-term, predictable, and consistent coverage for all Medicare beneficiaries.

HF is one of the top five health conditions affecting Medicare beneficiaries, with approximately 80% of HF patients being >65 years of age.[62,68] It is also the leading cause of hospitalization among older adults; and Medicare beneficiaries with HF have the highest readmission rate of any condition.[62] Much of the financial burden falls to Medicare, as an estimated three-quarters of emergency department visits and hospitalizations with primary or comorbid HF were among Medicare beneficiaries.[66] The magnitude of unmet need warrants access to meaningful interventions.

The CardioMEMS™ HF System measures pulmonary artery (PA) pressures to guide HF patient management, using a permanently implantable wireless sensor, a patient electronics system, and a secured patient database for clinician review. Trended hemodynamic data enables physicians to remotely adjust medications as a meaningful component of virtual medical care.

Abbott has worked collaboratively with CMS to best define the evidentiary requirements to support an NCD for remote hemodynamic monitoring for HF with the CardioMEMS™ HF System.

This began in May 2014 with the CHAMPION pivotal IDE trial, which formed the basis for FDA approval of the CardioMEMS™ HF System for wirelessly measuring and monitoring PA pressure and heart rate in NYHA Class III HF patients who have been hospitalized for HF in the previous year.[46]

The GUIDE-HF pivotal IDE trial was designed in partnership with CMS and FDA to further the evidence to support hemodynamic monitoring for HF. Completion of two randomized, pivotal IDE trials (CHAMPION and GUIDE-HF randomized arm), provides CMS an opportunity to review the comprehensive dataset supporting the FDA approved indication for NYHA Class II or III HF patients who either have been hospitalized for HF in the previous year and/or have elevated natriuretic peptides.

Since FDA approval in 2014, several real-world studies (including three prospective single-arm studies) have demonstrated consistency with the results from CHAMPION, demonstrating a positive treatment effect in

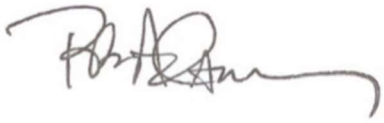
reducing HF rehospitalizations. These studies provided extensive safety evidence and further demonstrated that hemodynamic monitoring for HF is associated with overall reduction of PA pressure.

The clinical community supports an NCD that best defines the appropriate patient population proven to benefit from remote hemodynamic monitoring because the lack of clear coverage criteria leads to the misconception that the technology is investigational and experimental and non-covered by payers and Medicare. Although the Medicare contractors currently cover the CardioMEMS™ HF System based on reasonable and necessary guidelines (e.g., individual case consideration), this "silent/implicit" coverage does not provide reasonable long-term assurance or predictable coverage for providers and patients as it continues to generate questions on appropriate criteria based on the evidence that defines utilization for this technology. An NCD would provide predictable and consistent coverage for all Medicare beneficiaries (both traditional fee-for-service and Medicare Advantage Plans) given the totality of the evidence supporting the CardioMEMS™ HF System.

The attached request and appendices provide key information for CMS to develop an NCD for remote implantable hemodynamic monitoring for HF. The request includes information required by CMS to facilitate discussions on coverage as well as supporting information for patient selection criteria utilized to support the current and expanded FDA indications for the CardioMEMS™ HF System. We have also included our perspectives on the scope of the NCD and the questions that we believe should form the basis of the analysis of the clinical evidence.

Thank you for your consideration of this request. If you have questions, please feel free to reach out to me, James Hasegawa (James.Hasegawa@abbott.com) or Michael Baffoni (Michael.Baffoni@abbott.com) with the Abbott Health Economics & Reimbursement (HE&R) team.

Sincerely,



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Enclosures

Formal NCD Request for Remote Implantable Hemodynamic Monitoring for HF

CONTENTS

1. REQUEST

A. SCOPE

Abbott is requesting that CMS initiate a National Coverage Analysis (NCA) for the purpose of developing an NCD for remote hemodynamic monitoring for heart failure patients via an implantable device(s). We request that CMS limit its NCA and NCD to devices that meet this description, and which are FDA approved. This request for coverage is specific to the CardioMEMS™ HF System, which received FDA approval on May 28, 2014, and received FDA approval for an expanded indication on February 18, 2022. At the time of this request, the CardioMEMS HF System is the only FDA approved device for remote hemodynamic monitoring for heart failure patients. Currently Endotronix, Inc is conducting a prospective, multi-center, open label, single arm clinical trial to evaluate the safety and effectiveness of the Cordella PA Sensor System in NYHA Class III Heart Failure Patients with an estimated primary completion date of November 2022. More information can be found here: https://clinicaltrials.gov/ct2/show/NCT04089059

Pulmonary artery (PA) pressures are commonly measured via a Swan-Ganz catheter or right heart catheter in the hospital setting to manage heart failure.[1] In contrast to other device-based diagnostics, PA pressure measurements provide the physician with actionable information to effectively adjust medical therapy and provide education to improve adherence, as well as deploy other support that personalizes individual care needs early, before the traditional signs and symptoms of decompensation develop. However, prior to the availability of outpatient wireless PA pressure monitoring for heart failure, no other technologies existed to measure PA pressures remotely outside the hospital setting. Prospective clinical trials evaluating other telemonitoring strategies, which rely predominantly on early detection of heart failure signs and symptoms, and weight change as a marker of body volume or changes in systemic blood pressure, have repeatedly demonstrated no impact on hospitalization rates in the symptomatic patients studied.[2-10] Other means of telemonitoring for heart failure patients rely on signs and symptoms; none of these other methods relies on PA pressures. This NCD request is limited to analysis of evidence supporting coverage for New York Heart Association (NYHA) II or III HF patients who either have been hospitalized for HF in the previous year and/or have elevated natriuretic peptides who are candidates for an FDA-approved implantable remote hemodynamic monitoring system.

Based upon the body of peer reviewed published evidence, we encourage CMS to cover remote hemodynamic monitoring for NYHA Class II or III heart failure patients via implantable device that directly measures PA pressures, allows for continuous outpatient monitoring, and which has received a PMA from the FDA for the device's labeled indications. The current indications for use for the CardioMEMS HF System may be found below.

Abbott proposes that the Coverage & Analysis Group address the following pertinent question relating to evaluation of the ***CardioMEMS HF System***:

- Does the CAG agree that the evidence sufficiently demonstrates that implantation and use of a remote hemodynamic monitoring device improves health outcomes for Medicare beneficiaries who meet the FDA indication of NYHA Class II or Class III heart failure with either a prior heart failure hospitalization in the past 12 months and/or elevated natriuretic peptide levels?

B. BENEFIT CATEGORIES

Abbott considers the following CMS benefit categories to apply to this request:

- Physician services (SSA Section 1861(q), (r), and (s)(1))
- Inpatient hospital services (SSA Section 1861(b))
- Outpatient hospital services (SSA Section 1861(s)(2)(B); Medicare Benefit Policy Manual, ch. 6, § 20)
- Diagnostic services (SSA Section 1861(s)(2)(C); Medicare Benefit Policy Manual, ch. 6, § 20.4)
- Prosthetic device services (SSA Section 1861(s)(6); Medicare Benefit Policy Manual, ch. 15, § 120)
- Ambulatory surgical center services (Medicare Benefit Policy Manual, ch. 15, § 260)

2. FDA INFORMATION

On May 28, 2014, the FDA approved the PMA application for the CardioMEMS HF System. The FDA has posted the Summary of Safety and Effectiveness Data (SSED), the approval, Implant System Directions for Use, and the Patient Guide on its website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100045.

On February 18, 2022, the FDA approved the expanded indication PMA supplement for the CardioMEMS HF System. The FDA has posted the SSED, the approval, System Guide, and Patient System Guide on its website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100045S056

The Integrated Summary of Safety and Effectiveness Data can be found in the appendices. The original and expanded FDA indications can be found below.

A. INDICATIONS FOR USE

Expanded Indication:
The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.

Original Indication:
The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations.

The CardioMEMS HF System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one-month post implant.

B. PATIENT SELECTION CONSIDERATIONS

Abbott recommends patient selection considerations align with those for the GUIDE-HF pivotal IDE clinical trial.[12]

Remote implantable hemodynamic monitoring devices for heart failure are covered when the device has received Food and Drug Administration (FDA) Premarket Approval (PMA) for that device's FDA-approved indication and meet all of the following specifications indicated below:

- NYHA Class II or NYHA Class III heart failure symptoms predominantly present over the previous 30 days despite maximally tolerated guideline-directed medical and device therapies regardless of left ventricular ejection fraction (LVEF);
- Patients who are able to tolerate dual antiplatelet or anticoagulation therapy for one-month post implant;
- Patients should be within the anatomical considerations per the manufacturer's IFU for appropriateness of sensor functionality (e.g., body mass index (BMI), chest circumference)[a];
- At least one heart-failure-related hospitalization within the past 12 months

  OR

  An elevated NT-proBNP or BNP defined per manufacturer's IFU[b].

[a] Example from CardioMEMS IFU: Patients with a body mass index (BMI) < 35kg/m2. If BMI is ≥ 35 kg/m2 then, patient should have a chest circumference of < 65 inches

[b] Example from GUIDE-HF:

3. SUPPORTING MEDICAL AND SCIENTIFIC EVIDENCE

A. GENERAL BACKGROUND ON HEART FAILURE – DEFINITION AND BURDEN

I. HEART FAILURE DEFINITION

Congestive heart failure (HF) occurs when the heart muscle is damaged, which results in either weakness with an inability to propel blood forward or abnormal stiffness restricting the heart's ability to appropriately fill. These types of myocardial damage can cause an elevation in left ventricular pressures that are reflected back-line into the pulmonary circulation. Multiple diseases result in impaired heart function, but most commonly myocardial infarctions, valvular heart disease, hypertension and inflammation of the heart muscle, or myocarditis are causative. The term acute decompensated heart failure (ADHF) typically describes a change from a stable, chronic HF syndrome to unstable worsening symptoms of shortness of breath with minimal exertion or at rest. Many patients with ADHF require intravenous medical therapies while monitored in the hospital setting to re-establish clinical stability. When patients with chronic HF experience acute decompensation, the heart muscle may be further damaged and the cardiovascular system may worsen, leading to progression of heart impairment.

Several working definitions of HF have been formulated to develop clinical guidelines for diagnosis and treatment. The HFSA defines HF as "a syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and characterized by either left ventricular dilation or hypertrophy or both."[13] The American College of Cardiology Foundation / American Heart Association (ACCF/AHA) guidelines define HF as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood."[14] According to the European Society of Cardiology, diagnosable HF exists in patients who have both HF symptoms (e.g., breathlessness or fatigue) and signs (fluid retention, such as pulmonary congestion or ankle swelling), along with objective evidence of a structural or functional abnormality of the heart at rest (e.g., abnormal echocardiogram, cardiac murmurs).[15] General consensus in all guideline documents suggests that HF management goals should be focused on those medical and device therapies designed to prolong life and improve heart performance within months of diagnosis; and in preventing decompensation, which occurs when excessive volume buildup leads to symptoms of congestion and hospitalization. It is also consensus that congestive symptoms are associated directly with elevated cardiac filling pressures.

Direct and accurate assessment of cardiac filling pressures has been historically difficult to achieve for clinicians as previous means required invasive hospital-based procedures. Because of previous limitations in technology, physicians had to rely on surrogate markers to estimate volume status and cardiac filling pressures in order to guide therapy decisions. These surrogate markers, which are inherently non-specific for heart failure diagnosis, have included assessment of patient weight, systemic blood pressure and physical examination of jugular venous pressure when the physician sees the patient in clinic.

II. CLASSIFICATIONS OF HF

NYHA/AHA

According to the American Heart Association, the New York Heart Association (NYHA) Functional Classification System places patients in one of four categories based on how much they are limited during physical activity; and via an objective assessment of disease (Table 1).

- Subjects with LVEF ≤40%: NT-proBNP ≥1000 pg/mL (or BNP ≥250 pg/mL)
- Subjects with LVEF >40%: NT-proBNP ≥700 pg/mL (or BNP ≥175 pg/mL)
- Thresholds for NT-proBNP/BNP corrected for BMI using a 4% reduction per BMI unit over 25 kg/m2

Table 1. New York Heart Association Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity [16]
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

HFpEF/HFrEF

The two types of left ventricular heart failure – heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF) – are based on whether the ability of the left ventricle to contract, or to relax, is affected. HF may be associated with a wide spectrum of left ventricle (LV) functional abnormalities, which may range from patients with normal LV size and preserved Ejection Fraction (EF) to those with severe dilatation and/or markedly reduced EF. HFrEF, also referred to as systolic HF, is defined as an EF of ≤40. HFpEF, also referred to as diastolic HF, is defined as an EF of ≥50, and associated with good contraction of the heart muscle.[14] EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies[17] and because most clinical trials selected patients based on EF.

III. DISPARATE IMPACT ON HFPEF, WOMEN, AFRICAN AMERICANS

Treatment of HFpEF remains challenging. Unlike HFrEF, which has several well-established treatments supported by rigorous guidelines and a robust evidence base, HFpEF does not yet have a compelling evidence-based intervention proven to modify the natural history of this condition. The notable exception is spironolactone for which there are modest supportive data and a brief mention in the HF clinical practice guidelines. In the community, approximately 50% of patients with HF have HFpEF.[18] Women make up 63% of HF patients with HFpEF. Although HF is an important cause of morbidity and mortality for women, only 20% to 25% of subjects in randomized clinical trials are women.[19]

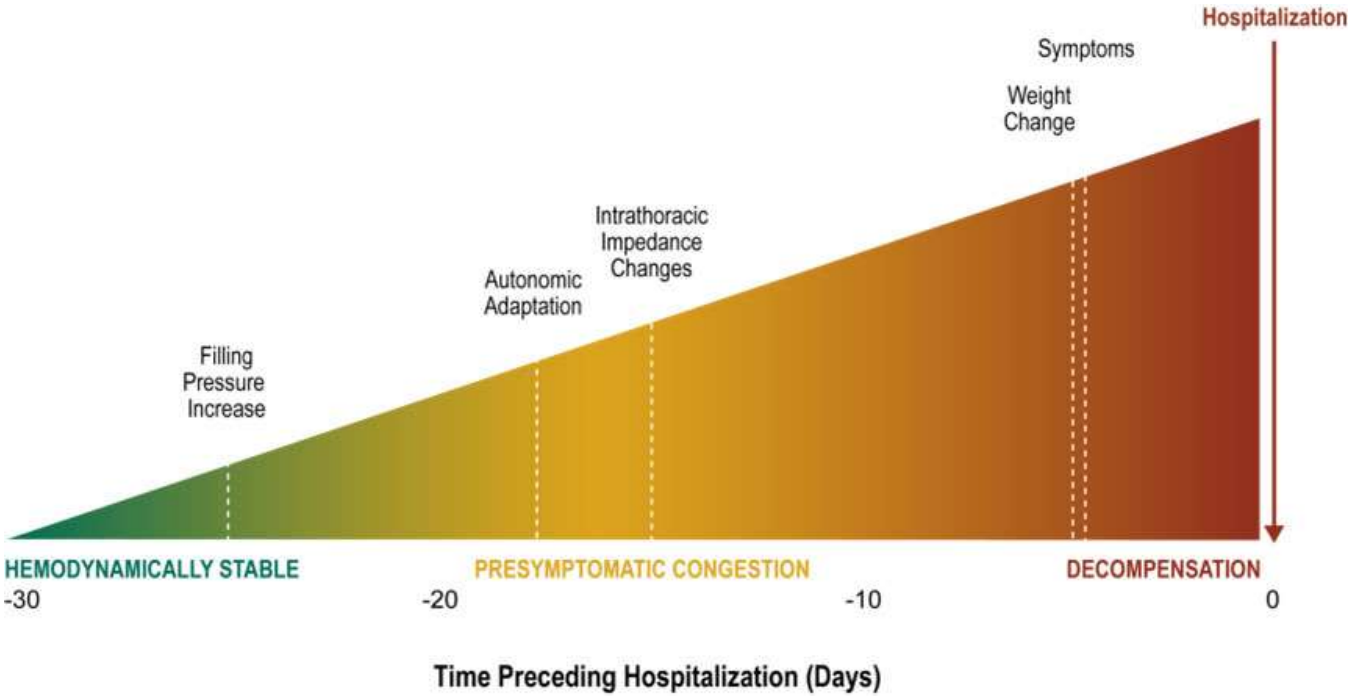
Not only are there challenges in treating HF in women, African Americans also have disparate HF outcomes. Compared with other race/ethnic groups, African American patients have the highest incidence and prevalence of heart failure as well as the worst clinical outcomes.[20,21] African American patients experience a 50% higher incidence of HF relative to the general population, as well as an increased risk of mortality secondary to chronic HF (CHF) as compared with White patients. The rate of HF hospitalization for African American men and women is nearly 2.5-fold higher when compared with Whites. While the relative rate of HF hospitalization has improved for other race/ethnic minorities, the disparity in HF hospitalization between African American and White patients has not decreased during the last decade.

IV. PATHOPHYSIOLOGY OF HF

Acutely decompensated heart failure (ADHF) is characterized by congestion, fluid retention and sometimes as inadequate cardiac output.[13] Without proper management, chronic stable HF can worsen and progress into ADHF, a condition associated with increased hospitalization rates and mortality.[22] Proper and timely diagnosis and disease management are vital to stabilize patients and prevent disease progression.[13] Diuretics are recommended for patients with clinical symptoms of fluid overload, including congestive symptoms or elevated filling pressures. However, physicians have historically lacked adequate tools to continually monitor intracardiac pressure, and thus detect pulmonary congestion prior to clinical decompensation.[23]

Illustrated below, early-stage HF may be asymptomatic, but may progress over time.[24] The mechanism of symptomatic and progressive HF is based on the body's response to an alteration in cardiac output or stroke volume. This abnormality is sensed in the aorta, carotid and renal arteries on a beat-to-beat basis, sending signals to the brain that circulatory impairment is threatening survival. The central nervous system processes this information and sends "emergency" notifications to the sympathetic nervous system in an attempt to increase heart rate and strength of heart contraction. In addition, the brain interprets decreased stroke volume as a state of volume depletion, such as dehydration or hemorrhage. As a result, hormonal signals are released in the form of angiotensin II, aldosterone and epinephrine with the goal of retaining fluid to restore normal volume. This misinterpretation of the signals can lead to progressive volume accumulation, which in turn causes worsening cardiac performance. Additionally, excess volume and pressures in the blood vessels causes fluid to "leak" from inside the vessels into the tissues of the body. As pressures build and tissue fluid increases, patients feel increasingly short of breath, fatigued with severe exertional limitation and swollen. Other ill effects include stimulation of fibrosis, which causes the heart to become weaker and stiffer, along with activation of "apoptosis" mechanisms leading to myocardial cell death.

Figure 1. Pre-Symptomatic Phases of HF Congestion (graph adapted from Adamson PB, 2009)[24]



The symptom that most commonly leads to hospitalization for worsening HF is shortness of breath, which is produced by fluid retention and/or fluid redistribution, both of which result in an increase in PA pressures.[25-29]

V. B-TYPE NATRIURETIC PEPTIDE AND ITS RELATION TO DECOMPENSATION EVENTS

B-type natriuretic peptide (BNP) is a hormone produced by the myocardium. N-terminal (NT)-pro hormone BNP (NT-proBNP) is a non-active prohormone that is released from the same molecule that produces BNP.[30] Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. These changes can be related to heart failure and other cardiac problems. Levels goes up when heart failure develops or gets worse, and levels goes down when heart failure is stable. In patients with acutely decompensated HF, measurement of BNP or NT-proBNP at the time of presentation is useful for establishing prognosis or disease severity. In a recent study, it was observed over a very wide range of BNP, subdivided into seven ranges, the risk of HFH increased nearly 26% for every doubling of the BNP value.[31] These differences persisted over time, with risk in 6 to 12 months 20% higher. The same findings were true for all-cause mortality. The risk of all-cause mortality increased nearly 31% for every doubling of the BNP value. This biomarker can be utilized as by physicians to identify those HF patients who may be at risk for decompensation and subsequent HFH.

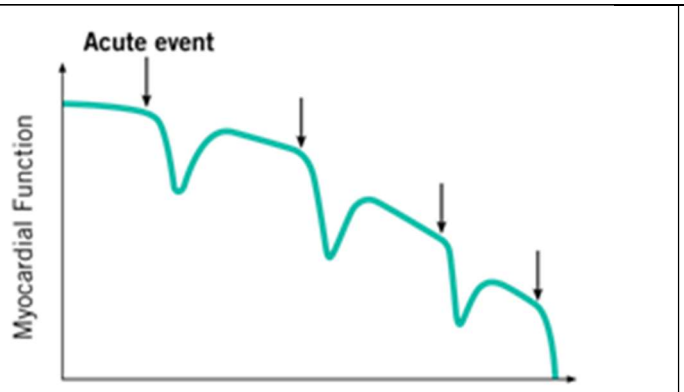
Prior to GUIDE-HF, elevated BNP had not been utilized as a risk predictor in PA pressure monitoring studies and its usefulness to identify patients who might benefit from PA pressure monitoring had not been established.[12]

VI. EFFECTS OF DECOMPENSATION ON MORBIDITY AND MORTALITY

Acute decompensation many times results in hospitalization, but HF patients experience myocardial injury and worsening of their HF syndrome, with increased mortality risk during the stress of volume overload.[22] Although overall death rates related to HF have improved in recent years, the 5-year mortality rate for HF remains 50%.[32] Data from the ADHERE registry revealed that, among patients with primary or secondary HF at hospital discharge, overall in-hospital mortality was 4.0%. This figure increased to 11% when patients treated only in the intensive care unit were evaluated.[22]

Multiple studies have demonstrated that decompensation events and HF hospitalizations cause permanent heart damage resulting in progressive dysfunction and worsening prognosis.[26,33,34] Early studies identified worsening cardiac function with each subsequent acute episode and demonstrated mortality is directly related to HF hospitalizations.

Figure 2. Worsening Heart Failure Leading to HF Hospitalizations Contributes to Disease Progression; HF Hospitalizations as a Predictor of Mortality

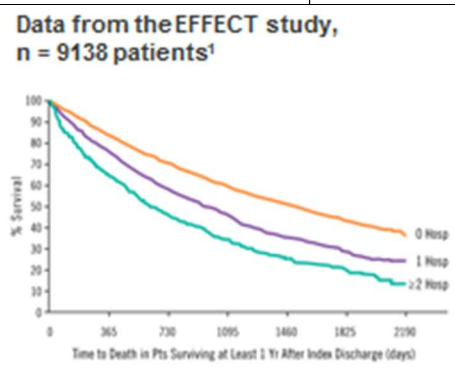


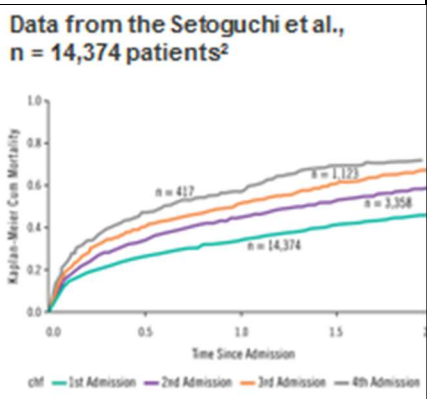
With each subsequent HF-related admission, a patient leaves the hospital with a further decrease in cardiac function.

Graph adapted from Gheorghiade M, et al. Circulation 2005.[26]

Studies show each admission decreases a patient's chance of survival.

Graphs adapted from Tu JV, et al. JAMA 200[33] *and Setoguchi S, et al. Am Heart J. 2007.*[34]

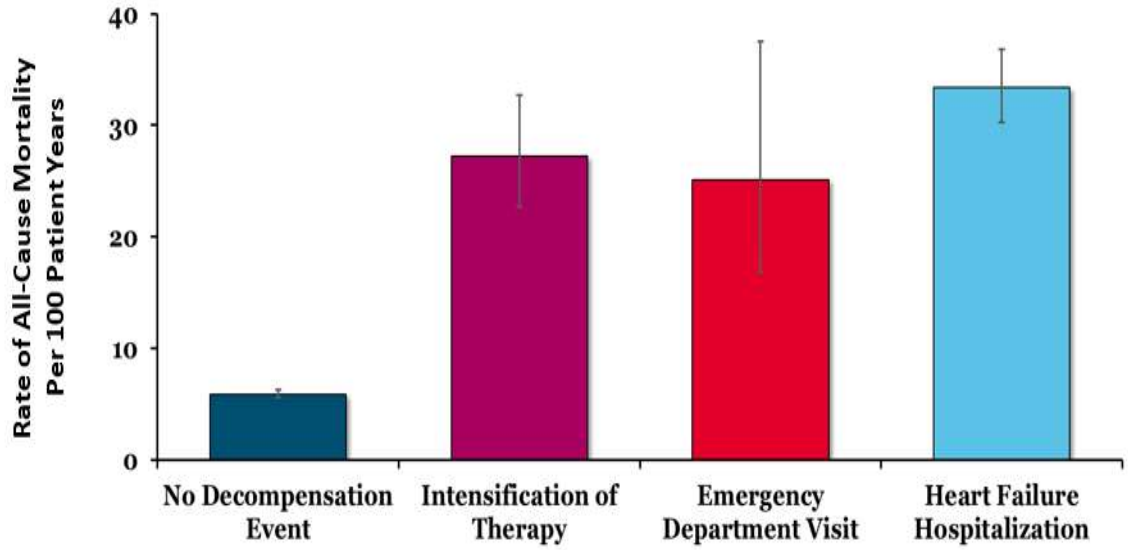




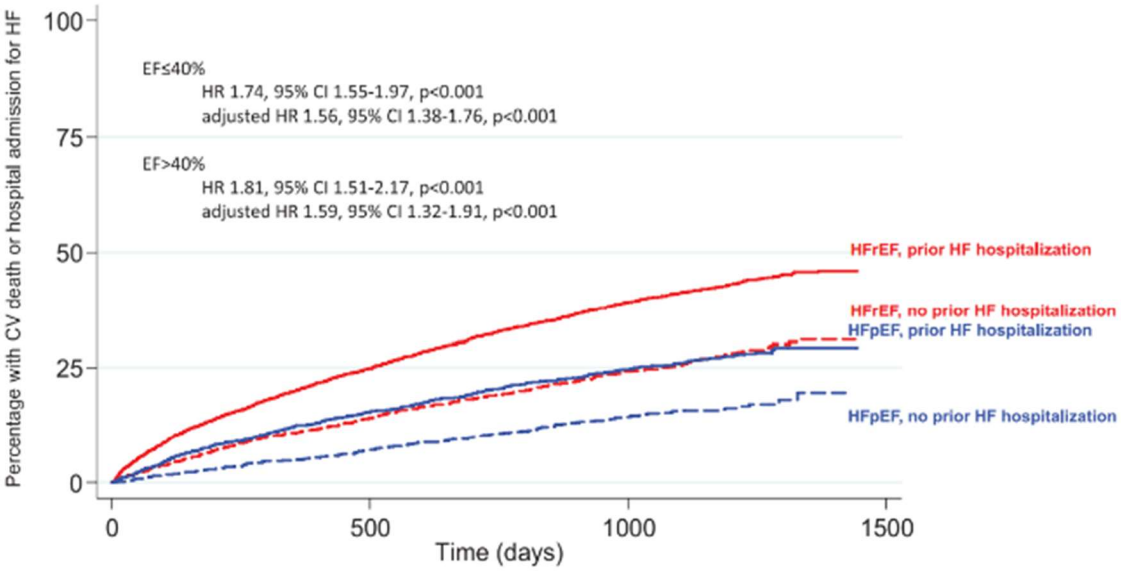
More recently, the PARADIGM trial taught us that the very act of decompensation -- regardless of where the rescue therapy is administered -- is associated with a 5 times increased risk of death during the follow-up period.[35] The risk of long-term death increased compared to those without decompensation. Decompensation events are associated with volume overload and congestion which lead to the need for increased intravenous rescue therapies, urgent visits, and hospitalizations. Bello et al, observed that previous hospitalization for HF is associated with increased risk of cardiovascular (CV) death and HF hospitalization independent of ejection fraction (EF).[36]

Figure 3. A: Decompensation Events Associated with Higher Mortality Risk.[35] B: Previous hospitalization for heart failure (HF) is associated with increased risk of cardiovascular (CV) death and HF hospitalization independent of ejection fraction (EF).[36]

A.



B.



VII. IDENTIFYING DECOMPENSATION AND PREVENTING HFH

The understanding of HF pathophysiology led to the development of specific drugs that antagonize this cascade of neural and hormonal activation. Neurohormonal antagonism with medical therapy has proven to prolong life and improve cardiac function. Neurohormonal signals to increase intravascular volume are continuous, however, and the effects of medications are variable making the specter of excess fluid accumulation and hospitalization always present.[37]

For many experienced physicians, HF signs and symptoms can be difficult to adequately assess, particularly in elderly and obese patients.[15] Tests used to confirm suspected HF decompensation include echocardiogram, laboratory tests and chest X-ray.[15,38] The main goal of long-term management of patients with heart failure is to understand the current volume status, as excess in intravascular volume is, by far, the most common reason for acute decompensation in these patients. Traditional tools are useful for the initial diagnosis of heart failure but lose value when assessing volume status in patients with chronic disease. Reliance on physical examination, laboratory testing or other clinical tools may lead to misjudgment of current volume status which may directly affect care leading to poor clinical outcomes.[39,40]

The standard of care which includes body weight and blood pressure is the traditional method for monitoring chronic HF. Studies have demonstrated that weight change cannot reliably be used as an indicator of rising pressures. Data from Lewin et al. showed that an absolute weight gain of 2 KG (or a relative weight gain of 2%) over 48-72 hours had poor sensitivity (only 9% and 17%) for acute decompensation.[41] Data from the FAST trial showed that at the nominal weight gain threshold of 3lbs in 1 day or 5 lbs. Within 3 days, sensitivity for decompensation was 22.5% (ranging from 12.5% to 37.1%).[42] These data demonstrate that increases in body weight in isolation are not sensitive in assessing clinical deterioration in established heart failure. The standard of care has not been able to portend episodes of decompensation based on multiple trials (TELE-HF, TIM-HF, TEN-HMS, BEAT-HF DOT-HF, and REM-HF) that evaluated signs and symptoms and impact on hospitalization. The inability of HF clinicians to reduce HFH using the standard of care in these patients demonstrates the struggle HF clinicians experience to successfully manage chronic HF patients because the standard of care is significantly less sensitive and specific than hemodynamic monitoring.

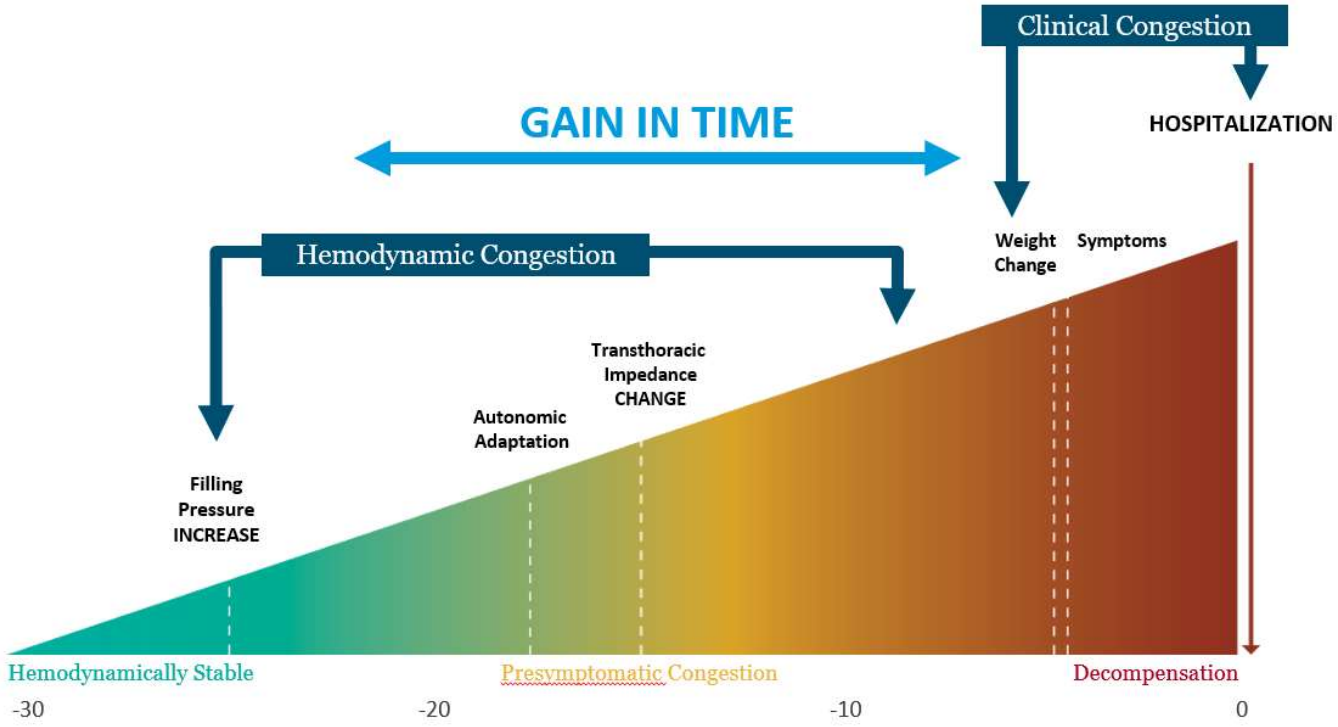
Table 2. Monitoring HF Decompensation and the effects on HF Hospitalization

Trial	N	Parameter Monitored	Impact on HF Hospitalization	Journal
TELE HF[2]	1,653	Signs/symptoms, daily weights	None	The New England Journal of Medicine, 2010
TIM HF[3]	710	Signs/symptoms, daily weights	None	Circulation, 2011
TEN HMS[4]	426	Signs/symptoms, daily weights, BP, nurse telephone support	None	Journal of the American College of Cardiology, 2005
BEAT HF[5]	1,437	Signs/symptoms, daily weights, nurse communications	None	American Heart Association 2016
INH[6]	715	Signs symptoms, daily weights, telemonitoring, nurse coordinated DM	None	Circulation Heart Failure, 2012
DOT HF[7]	335	Intrathoracic impedance with patient alert	Increased	Circulation, 2011
Optilink[8]	1,002	Intrathoracic impedance	None	European Journal of Heart Failure, 2011
REM HF[9]	1,650	Remote monitoring via ICD, CRT-D or CRT-P	None	European Society of Cardiology, 2017
MORE CARE[10]	856	Remote monitoring of advanced diagnostics via CRT-D	None	European Journal of Heart Failure, 2016
Total	**8,793**	**MULTIPLE TRIALS, > 8,500 PATIENTS: No reduction in HF hospitalizations**		

In contrast, the CardioMEMS HF System provides real-time data regarding patients' PA pressure, which accurately reflects volume state. Persistently high PA pressures are associated with high risk for subsequent hospitalizations. This gave rise to the hypothesis that patient stability could be maintained by monitoring filling pressures and maximizing medical therapies to keep pressures controlled. This strategy requires lowering baseline pressures by adjusting vasoactive medications (diuretics and vasodilators) based on the observation that lower PA pressures lead to lower hospitalization risk. The target of this therapeutic intervention is to lower PA pressures to target ranges and is initiated without waiting for development of HF symptoms. The second component of this strategy requires providers to respond to changes from new chronic baseline pressures.

Monitoring the actual pressure in the PA allows health care providers the opportunity to better manage presymptomatic congestion leading to earlier intervention and prevention of hospitalization. As illustrated in Figure 4, pre-symptomatic intervention with hemodynamic congestion facilitates proper diuretic dosing and adjustments, a cornerstone in ADHF therapy.[43] PA pressure provides an earlier indicator of HF progression than other markers.[24] Ongoing monitoring of PA pressure, used in conjunction with clinical signs and symptoms, provides an opportunity to personalize medication dosages for each individual patient.[11,12,44,45] This approach was proven to be a superior means to reduce HF hospitalizations, as well as improve patient outcomes compared to clinical signs and symptoms alone. [11,12,44,45]

Figure 4. Identification of Congestion with Hemodynamic Monitoring vs. Clinical Signs and Symptoms



B. CARDIOMEMS™ HF SYSTEM: DEVICE OVERVIEW

The CardioMEMS HF System was approved through the Premarket Approval (PMA) process by the U.S. FDA in May 2014.[46] While there were concerns related to sponsor communications, in reviewing the CHAMPION trial and additional analyses, the FDA concluded, "… the device has been shown to be very safe, and the totality of the effectiveness data consistently points to a positive treatment effect."

On February 18, 2022, the CardioMEMS HF System expanded indication was approved by the FDA via a PMA supplement. Use of the implant and system is indicated for wirelessly measuring and monitoring PA pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides.[69] The system allows for wireless measurement and monitoring of PA pressure, with a small sensor placed within the PA. Physicians use the hemodynamic data reported through the CardioMEMS HF System for heart failure management with the goal of controlling PA pressures and reducing heart failure hospitalizations. The CardioMEMS HF System is for a well-defined patient population and is not appropriate for NYHA Class IV patients. The system is also contraindicated for patients who have an inability to take dual antiplatelet drugs or anticoagulants for one-month post-implant.

I. TECHNOLOGY DESCRIPTION

Manufactured by Abbott, the CardioMEMS HF System includes 3 main components:

- Implantable wireless sensor with delivery catheter
- Patient Electronics System
- Patient database for clinician review (CardioMEMS HF System website)

Figure 5. The CardioMEMS HF System Components

The small sensor (15mm x 3.4 mm x 2 mm) is a patented microelectromechanical system (MEMS) that consists of a metallic coil that serves as an antenna and a pressure sensitive capacitor fused between two hermetically sealed wafers transduces externally delivered radiofrequency energy into pressure information using a pressure sensitive capacitor in the sensor. Pressure on the capacitor alters the resonant frequency of the externally emitted RF energy in a linear relationship which is detected by the external antenna. This allows the sensor to function using externally transmitted energy rather than an implanted lead or battery.

Patients' transmission of data through their home electronics unit includes a monitor, wand, and pillow with sensory capabilities to power and interrogate the device. The online secured database provides daily information to the clinician and care team, including alerts sent to the physician based upon outputs programmed and tailored for the individual patient.

The wireless sensor is designed for permanent implantation into the distal PA. Once implanted, the CardioMEMS PA Sensor provides noninvasive hemodynamic data that are typically collected in the physician's office, clinic, hospital or patient's home (and transmitted to the treatment physician for review and appropriate action). The data provided by the HF system includes:

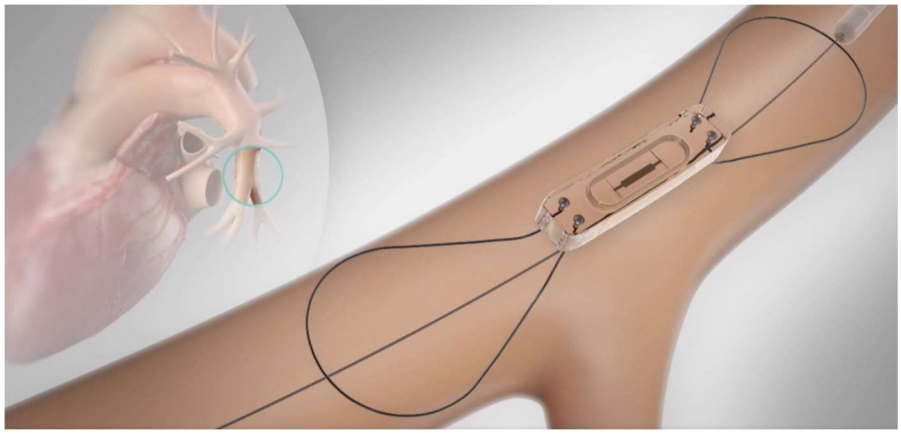
- PA pressure waveform
- Systolic, diastolic, and mean PA pressures
- Heart rate

Detailed system specifications are included in the CardioMEMS HF System Guide. Descriptions are also available in the CardioMEMS HF System User's Manual, patient data management and user guides (see Appendices). Hemodynamic data are transmitted to a secure website that serves as the patient database so that PA monitoring information is available at all times through the Internet. Changes in PA pressure are used in conjunction with HF signs and symptoms to guide adjustments to medications. Use of this data from this monitoring tool has been shown to change clinician behaviors, including timely adjustments to medical therapy, patient education and management.

II. CARDIOMEMS HF SENSOR IMPLANT PROCEDURE

Implanting the PA pressure sensor, shown in Figure 6, is a catheter-based procedure and is performed during routine right heart catheterization. The procedure requires approximately one hour to complete, and patients are typically awake under mild sedation. Interventional cardiologists, electrophysiologists, HF specialists or any cardiologist trained to perform right heart catheterization may implant the CardioMEMS pressure sensor. In addition, to implant the CardioMEMS HF System physicians must have a fluoroscope with digital angiography and the ability to record and recall images, radiopaque contrast media, and blood pressure monitoring equipment used for right heart catheterization.

Figure 6. Implantation of the PA Pressure Sensor



To implant the device, physicians typically access either the femoral vein or internal jugular vein, percutaneously using the Seldinger technique. Using the delivery system, the clinician introduces the pressure sensor to the PA using fluoroscopy guidance. A limited pulmonary angiogram is performed to confirm target vessel positioning and size. The over-the-wire delivery system allows deployment of the sensor by pulling a tether wire to release the sensor from the catheter. Two nitinol loops extending from the pressure sensor hold the sensor in place within the PA (Figure 6). The clinician calibrates the sensor using simultaneously acquired PA pressure readings obtained from a right heart catheter.

After implantation, patients restart anticoagulant therapy. Patients who were not prescribed anticoagulant therapy before the PA pressure sensor implant are required to take dual antiplatelet therapy or higher-level anticoagulation (DOAC or warfarin) if indicated for one month after implantation. After one month, patients continue a daily regimen of aspirin to reduce the likelihood of thrombosis.

Before hospital discharge, nurses train patients and/or caregivers on how to set-up and use the home electronics system. Physicians instruct patients on how frequently they should take a reading. To take and transmit a PA pressure reading requires approximately two to three minutes. To take a reading, patients position the antenna (preassembled in a pillow) on a flat surface four to five feet away from the home electronics unit, turn on the unit using the power button located on the back of the unit and lay on the pillow. Throughout the process the home electronics unit uses audible prompts to guide patients. To initiate a PA pressure reading, patients press a button on a small remote connected to the home electronics unit with a wire. When patients initiate a reading, the electronics unit assesses the signal strength between the sensor and the antenna. The home electronics unit automatically transmits the PA pressure information to a secure website and automatically turns off.

III. STANDARDS FOR THE FREQUENCY OF MONITORING

In general, the goal is for patients to upload every day and have qualified healthcare provider review weekly.

This is consistent with the requirements of the PA pressure remote monitoring CPT code 93264.[47] In general, weekly monitoring is acceptable so long as the patient maintains acceptable PA pressure (opti-volemic).

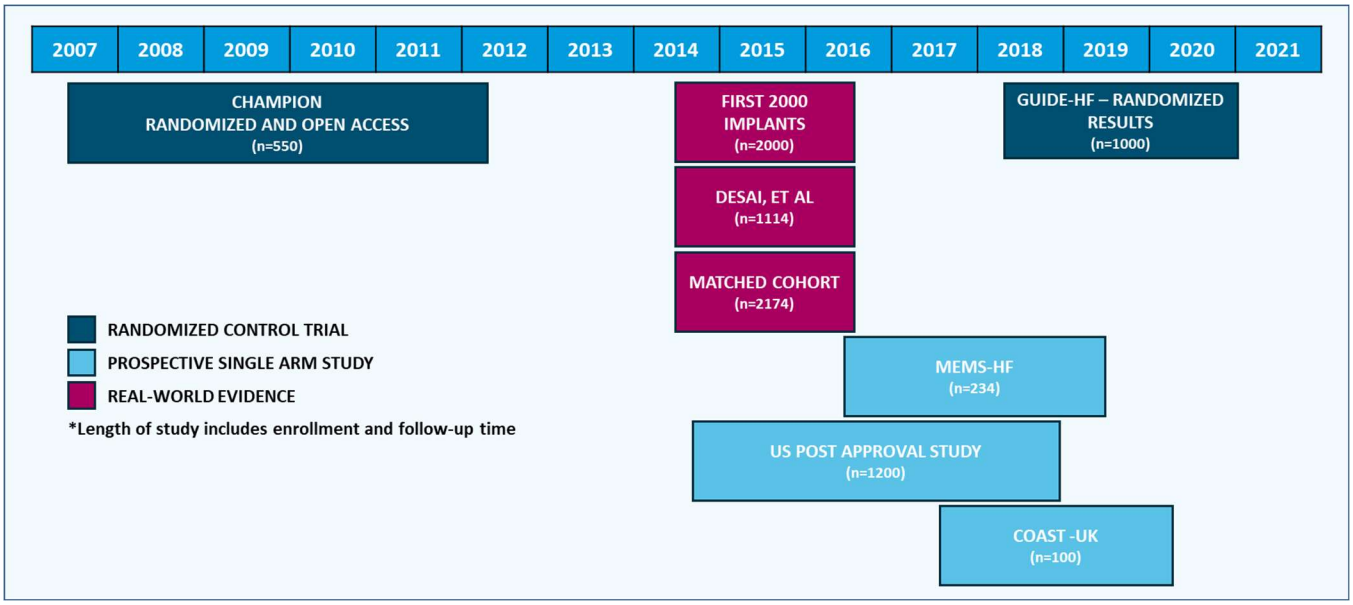
If PA pressure is not opti-volemic:

- Monitoring may be more frequent until opti-volemic in cases where the patient has elevated PA pressure (hyper-volemic) or low PA pressure (hypo-volemic); and
- Monitoring must occur at least 2–3 times per week until pressure stabilizes in cases where the patient receives medication modifications or exhibits significant deviations in trend data.

Qualifying facilities and clinical teams must certify to their ability and commitment to meet these monitoring requirements and must document the required monitoring in the applicable patient record.

C. SUPPORTING CLINICAL EVIDENCE

I. OVERVIEW



Abbott has worked collaboratively with CMS to best define the evidentiary requirements to support a national coverage determination (NCD) for remote hemodynamic monitoring for Heart Failure with the CardioMEMS™ Heart Failure (HF) System.

This journey began in May 2014 with the CHAMPION pivotal IDE trial, which formed the basis for FDA approval of the CardioMEMS™ HF System for wirelessly measuring and monitoring PA pressure and heart rate in NYHA Class III heart failure patients who have been hospitalized for heart failure in the previous year.[46]

The CHAMPION Trial was developed as single-blind study because the hypothesis being tested required investigators to review remotely uploaded PA pressures and actively change medical intervention to control them. This methodological necessity coupled with select instances of additional communications with study subjects led to the allegation that bias influenced the CHAMPION trial results.

To address this concern, Abbott in conjunction with the FDA conducted and evaluated an expanded analysis of the CHAMPION trial to determine the influence and impact of nurse communications in terms of characterizing and quantifying the results observed in the trial's treatment group.

Even though each of the analyses have inherent methodological limitations, the totality and direction of evidence all pointed towards the effectiveness of the CardioMEMS system. In reviewing the CHAMPION trial and the additional analyses, the FDA concluded, "… the device has been shown to be very safe, and the totality of the effectiveness data consistently points to a positive treatment effect."

Since FDA approval, several real-world studies (including three prospective single-arm studies) have demonstrated consistency with the results from CHAMPION, demonstrating a positive treatment effect in reducing HF rehospitalizations. These results have been reproducible within the British, Dutch, Irish, and German healthcare systems, indicating that the efficacy of PA pressure monitoring remains even within the different care pathways experienced by HF patients across these countries. These studies provided extensive safety evidence and further demonstrated that hemodynamic monitoring for heart failure is associated with overall reduction of PA pressure and clinicians are using the hemodynamic information to manage their patient's PA pressures.

A MEDCAC Panel convened in 2017, that evaluated the relevant endpoints to support heart failure trials, emphasized that the goal of managing HF was primarily focused on surrogates that helped prevent decompensations. With this goal in mind, Abbott worked in partnership with CMS and FDA to develop the GUIDE-HF pivotal trial to examine the hypothesis that hemodynamic-guided care with CardioMEMS will benefit a broader range of patients- particularly focusing on those with NYHA Class II and IV HF- and including those with congestion, but no previous hospitalization (patients with elevated natriuretic peptides).

The GUIDE-HF trial also addressed several other questions, including the reproducibility of the effectiveness of CardioMEMS with longer-term, 12-month follow up and whether there was a trend towards improved mortality and quality of life.[48]

Abbott worked closely with FDA and CMS to design the GUIDE-HF IDE trial. During these study design discussions, it was agreed that single blinding of both the treatment and control arms was appropriate because of the need for clinicians to access pressures in the treatment arm to validate the efficacy of hemodynamic care. Given the previous bias concerns related to the CHAMPION results, this single-blinded study design incorporated a tightly managed nurse communication protocol to ensure masking of the treatment and control arms.

GUIDE-HF demonstrated that hemodynamic-guided management across the spectrum of ejection fraction and symptom severity was safe and, in a pre-COVID-19 sensitivity analysis, a benefit of hemodynamic-guided management on the primary outcome, driven by a decrease in heart failure hospitalizations, was demonstrated. The primary endpoint results were consistent across multiple subgroups, including those defined by left ventricular ejection fraction, sex, previous heart failure hospitalization, and race. A treatment effect was observed in patients with mild to moderate (NYHA functional Class II–III) heart failure, and the results were consistent with observations from other trials.

The following section is a summary of clinical evidence across major studies evaluating the safety and efficacy of PA pressure monitoring.

II. SUMMARY OF CLINICAL DATA

As summarized below, results from the GUIDE-HF and CHAMPION clinical trials, the CardioMEMS Post Approval Study, the European MEMS-HF study, the COAST-UK study and multiple retrospective studies have consistently demonstrated PA pressure monitoring improves clinical outcomes.

Table 3. Summary of PA Pressure Monitoring Studies

Study	Authors' Conclusion
Randomized Control Studies	
GUIDE-HF[12] Lindenfeld J, et al. Lancet. 2021	Hemodynamic-guided management across the spectrum of ejection fraction and symptom severity was safe and, in a pre-COVID-19 sensitivity analysis, a benefit of hemodynamic-guided management on the primary outcome, driven by a decrease in heart failure hospitalizations, was demonstrated. The observed reduction in heart failure hospitalizations was identical to the 28% decrease reported for patients with NYHA functional Class III heart failure in the CHAMPION trial and consistent with reports of other observational studies, including the CardioMEMS US Post-Approval Study, and clinical trials reporting the benefits of hemodynamic-guided monitoring. Reductions in PA pressure and heart failure hospitalizations, both of which have been previously associated with a reduction in mortality were observed. These data affirm and expand the evidence base supporting the benefits of hemodynamic-guided management in patients with chronic heart failure and suggest that such an intervention might be applicable to a broader range of patients, including those with mild to moderate heart failure and those with elevated natriuretic peptides and no previous heart failure hospitalizations.
CHAMPION[11,45] Abraham WT, et al. Lancet. 2011 Abraham WT, et al. Lancet. 2016	Patients whose HF treatment decisions were based on hemodynamic monitoring data obtained from the CardioMEMS HF System experienced a statistically significant 28% relative risk reduction in HF-related hospitalizations as compared with control group patients at 6 months and had a 33% reduction in HF-related hospitalizations over the study duration (average follow-up 18 ± 7 months).

	The reduction in the need for admission to hospital, both all-cause and heart failure related, seen during the first 6 months was maintained during longer randomized access follow-up and subsequently during open access in which adjustment of therapy was no longer monitored by study staff protocol. The totality of evidence supports the concept that PA pressure-guided heart failure management is superior to clinical assessment alone in heart failure patients with persistent symptoms following admission to hospital.
Single Arm Prospective Studies	
Post-approval Study: US[55]	The evidence confirmed in the U.S. PAS continues to further support the findings that CardioMEMS™ promotes reduced HFH and PA pressure reductions across a larger cohort. The U.S. PAS data also is a significant driver in proving safety outcomes with 1,200 patients showing a greater than 99% freedom from DSRC. The frequent transmission activity also provides a secondary benefit of continued patient engagement with healthcare providers.
MEMS-HF European Study[54]	The CardioMEMS™ HF system proved to be a safe and reliable tool to help patients treat and reduce PA pressures over time as confirmed in U.S. studies. Like the U.S., favorable clinical outcomes proved to be true in the health systems of Germany, Ireland, and The Netherlands including reduced PA pressure, fewer HF hospitalizations, high survival and an added metric of improved quality of life and fewer depressive symptoms.
COAST-UK Registry[70]	The results reported here are entirely consistent with those in other large studies with similar design and support the usefulness of PA pressure monitoring as a management strategy superior to usual clinical care. The COAST-UK demonstrates that PA pressure-guided therapy is safe and feasible, with a high likelihood of achieving meaningful clinical benefits, in the UK National Health Service system. Remote PA pressure monitoring is an opportunity to intensify and improve HF management and outcome in an era that heavily relies on virtual and remote encounters.
Retrospective Studies	
Desai et al.[52]	In the 6-months before implantation, the 1114 patients had 1020 HF hospitalizations, and in the 6-months following CardioMEMS™ implant there were 381 hospitalizations. The significant reduction in hospitalization frequency was sustained to 1-year after CardioMEMS™ implant. These data provide real-world evidence supporting the incremental value of this approach to HF management. The observation of sustained cost reductions out to one year in a real- world population supports the concept that the benefits of hemodynamic monitoring are durable over longer term follow up, a factor that is essential for long-term cost-effectiveness.
First 2000 Commercial Implants[51]	An analysis of PA pressure trends and transmission adherence was performed in the first 2000 patients after commercialization with at least 6 months of follow-up data. This study provides very important analyses demonstrating that hemodynamic-guided HF management with an implanted PA sensor is generalizable to the normal clinical management of patients with symptomatic HF. Long-term patient acceptance and adherence are clearly demonstrated by an average of 1.2 days between remote pressure transmissions and >98% weekly use of the system. The goal of remote PA pressure monitoring is to incorporate the pressure information in decision making leading to medical intervention expressly to lower pressures. The current data, in the first consecutive 2000 patients managed with PA pressure information for at least 6 months, demonstrate that pressures were significantly lower compared with baseline.
Contemporary Control: Propensity Matched Outcomes[53]	The findings in this large retrospective study are consistent with results of other studies. HF patients implanted with a CardioMEMS™ HF System had lower rates of mortality and HF Hospitalization at 12 months than their matched control cohort, conveying the use of hemodynamic monitoring improves HF outcomes.

Efficacy

Heart failure hospitalizations

Reduction in heart failure hospitalizations (HFH) has been consistently demonstrated across RCTs, prospective single arm studies, and propensity matched cohorts, representing over 5000 patients implanted and monitored with the CardioMEMS HF System. GUIDE-HF established that the treatment effect extends to patients with mild to moderate HF as well as those without a previous HFH. GUIDE-HF, CHAMPION, and the propensity-matched analyses demonstrated a reduction in HFH in the treatment arm vs. the control while MEMS-HF, US Post-Approval

Study, and COAST-UK studies showed reductions in HFH in the 12 months post-implant relative to the 12 months prior to implant.

Table 4. Effect of PA Pressure Monitoring on HFH Across the Studies

Study	N	Follow up	HFH Reduction	p value
Treatment vs Control Studies				
RCT: GUIDE-HF[12]	1000	12 mo.*	28%	p < 0.01
RCT: CHAMPION IDE[11,45]	550	18 mo.	33%	p < 0.0001
Contemporary Control: Propensity Matched Outcomes[53]	2174	12 mo.	24%	p < 0.001
1 Year Post-Implant vs 1 Year Pre-Implant Studies				
MEMS-HF European Study[54]	234	12 mo.	62%	p < 0.0001
Post-approval Study: US[55]	1200	12 mo.	57%	p < 0.0001
COAST-UK Registry[70]	100	12 mo.	82%	p < 0.0001

**Pre-COVID Analysis: Median follow-up in the pre-COVID analysis was 8.6 months*

Reduction of PA Pressures – Area under the curve (AUC)

Active treatment of PA pressures through hemodynamic monitoring is central to avoiding decompensation events. GUIDE-HF and CHAMPION showed a greater reduction in PA pressures in the treatment arm vs the control. The CardioMEMS PAS, MEMS-HF, and the first 2000 commercial implants observed reductions in PA pressures vs baseline.

Table 5. Effect of PA Pressure Monitoring on Reduction of PA Pressures Across the Studies

Study		N	Follow up	PA Pressure Change (mm Hg×days)	p value
RCT: GUIDE-HF[12]	Treatment	497	12 mo.	-518.0	p = 0.014
	Control	503		-324.2	
RCT: CHAMPION IDE[11]	Treatment	270	6 mo.	-156.0	p = 0.008
	Control	275		+33.0	
First 2000 Commercially Implanted[51]		2000	6 mo.	-434.0	p < .0001
MEMS-HF European Study[54]		227	12 mo.	-1827.7	p < .0001
Post-approval Study: US [55]		1200	12 mo.	−790.9	p < .0001
COAST-UK Registry[70]		100	12 mo.	-1132.7	p < .0001

Quality of Life

KCCQ: The MEMS-HF study observed a 12.7-point increase (p<0.0001) at 12 months.[54] GUIDE-HF also saw an improvement in KCCQ-12 scores vs baseline at 6 and 12 months.[12]

EQ-5D-5L: MEMS-HF observed a 6.1-point increase (p=0.0002) at 12 months vs baseline in the "Visual Analogue Score).[54] The treatment group GUIDE-HF also saw a similar increase in EQ-5D-5L vs baseline.[12]

PHQ-9: MEMS-HF observed a 2.1-point improvement (p<0.0001) at 12 months vs baseline.[54]

Minnesota Living with Heart Failure Questionnaire: The CHAMPION Clinical Study observed that the average total score in the Treatment group at 6 months was 45 ± 26, which was significantly better than the average total score

in the Control group of 51 ± 25 (p = 0.02).[11] Similarly, a significantly better score was also demonstrated at 12 months in the Treatment group than the Control group (47.0 vs. 56.5, p=0.027).[45]

Safety

Amongst the total 3147 subjects evaluated in CardioMEMS trials to date, freedom from device or system-related complications was 99.2%, demonstrating a strong safety profile of the device and implantation procedure.

Table 6. Safety Profile Across the Studies

Trial	Patients	Freedom from DSRCs % (n/N)
RCT: GUIDE-HF[12]	1022	99.2% (1014/1022)
RCT: CHAMPION IDE[11]	575	98.6% (567/575)
Post-approval Study: US[55]	1,214	99.7% (1210/1214)
MEMS-HF European Study[54]	236	98.3% (232/236)
COAST-UK Registry[70]	100	100% (100/100)
Total:	**3,147**	**99.2% (3123/3147)**

Patient Compliance

With technologies such as the CardioMEMS HF System, patient compliance with data transmission is an important component in enabling clinicians to successfully manage their patients with heart failure. Prospective trials and retrospective analyses have demonstrated consistent weekly patient transmissions, which is also one of the requisites for physician billing of CPT code 93264, with over 80% of patients providing daily transmissions of their PA pressures one year post implant.

Table 7. Patient Compliance with Weekly/Daily Transmissions of PA Pressures Across the Studies

Trial	Patients	Duration Assessed	Compliance Rate (median unless otherwise noted)
RCT: GUIDE-HF[12]	1,000	12 mo.	**Daily: 80 – 90%** (mean, both treatment & control)
First 2000 Commercially Implanted[51]	2,000	Patients with ≥ 6 mo. of data	**Daily: 98.6%** [range: 82.9 – 100%]
			1.27 days (avg time btw transmissions)
Post-approval Study: US[55]	1,200	12 mo.	**Daily: 85%** [no range provided]
			Weekly: 100% [no range provided]
MEMS-HF European Study[54]	234	12 mo.	**Daily: 87.6%** [range: 69.4 – 94.9%]
			Weekly: 97.2% [range: 88.6 – 100%]
COAST-UK Registry[70]	100	12 mo.	**Daily: 85.9 ± 19.3%** (mean)
			Weekly: 94.5 ± 14.2% (mean)

Thorough descriptions and the key results of the studies referenced above can be found at the end of the submission as part of the appendices and will be represented in chronological order. We believe that the presentation of the evidence to date strongly supports an NCD that establishes optimal coverage for remote hemodynamic monitoring in appropriate Medicare beneficiaries.

III. ONGOING STUDIES

As of the submission of this request, four PA pressure monitoring studies are currently ongoing:

- The GUIDE-HF Observational Single Arm study will test the hypothesis that hemodynamic-guided care is similarly effective in HF patients enrolled based on elevated natriuretic peptide levels as in those with a prior HFH within 12 months. More information can be found at: https://clinicaltrials.gov/ct2/show/NCT03387813
- The PROACTIVE-HF IDE Trial is a prospective, multi-center, open label, single arm clinical trial to evaluate the safety and effectiveness of the Cordella PA Sensor System in NYHA Class III Heart Failure Patients with an estimated primary completion date of November 2022. More information can be found at: https://clinicaltrials.gov/ct2/show/NCT04089059
- The PASSPORT-HF trial is a German prospective, randomized, open, multicenter trial evaluating the effects of a hemodynamic-guided, HF nurse-led care approach using the CardioMEMS™ HF-System on clinical end points, safety, and quality of life. The target population consists of heart failure (HF) patients who have been predominantly in New York Heart Association (NYHA) Stage III for the past 30 days and were admitted to the hospital at least once in the past 12 months for HF. More information can be found at: https://clinicaltrials.gov/ct2/show/NCT04398654
- The MONITOR-HF trial is a Dutch prospective, multi-center, randomized clinical trial in 340 patients with chronic HF (New York Heart Association functional class III) randomised to HF care including remote monitoring with the CardioMEMS PA sensor or standard HF care alone. The MONITOR HF trial will evaluate the efficacy and cost-effectiveness of haemodynamic monitoring by CardioMEMS in addition to standard HF care in patients with chronic HF. Clinical Trial Registration number NTR7672.

4. BENEFITS AND RELEVANCE TO MEDICARE POPULATION

Heart failure is one of the top 5 health conditions for Medicare beneficiaries. HF is the leading cause of hospitalization among older adults, and Medicare beneficiaries with HF have the highest readmission rate of any condition.[62] An analysis of the National Readmission Database was utilized to identify HF hospitalizations between 2010 and 2017.[63] Of the over 6.6 million HF readmissions that took place during the 15 months the study reviewed, 77% were attributable to Medicare beneficiaries. The Centers for Medicare & Medicaid Services' (CMS) Chronic Conditions Data Warehouse indicates that 14.5% of Medicare fee-for-service (FFS) beneficiaries had a diagnosis of heart failure in 2018.[64] The annual median total medical costs for heart failure care are estimated at $24,383 per patient, with heart failure-specific hospitalizations driving costs (median $15,879 per patient).[65] Much of the financial burden falls to Medicare, as an estimated three-quarters of ED visits and hospitalizations with primary or comorbid HF were among Medicare beneficiaries.[66]

In fact, CMS recognized the substantial improved clinical benefit of patients monitored with CardioMEMS when it granted this technology both a New Technology Add-on Payment and Transitional APC Pass-Through Payment in the 2015 inpatient and outpatient hospital system Final Rules. The application for approval of either type of incremental reimbursement mechanism requires demonstration of a "substantial clinical improvement" over current, available therapies to treat the condition or disease.

Use of the CardioMEMS HF System for NYHA Class II and III HF patients offers significant benefits to Medicare beneficiaries, providers, and the healthcare system.

The **GUIDE-HF** clinical trial was developed based on CMS/MEDCAC feedback in 2017. In the randomized arm of the trial, 74% of the enrollees were of Medicare age (≥65 yr). The treatment effect in the pre-COVID 19 analysis was shown to be greater in patients above the median enrollee age of ≥71 yr (n=508, HR 0.70, 95% CI 0.5 – 0.97, p=0.030). The trial demonstrated the utilization and benefit of PA pressure monitoring might be applicable to a

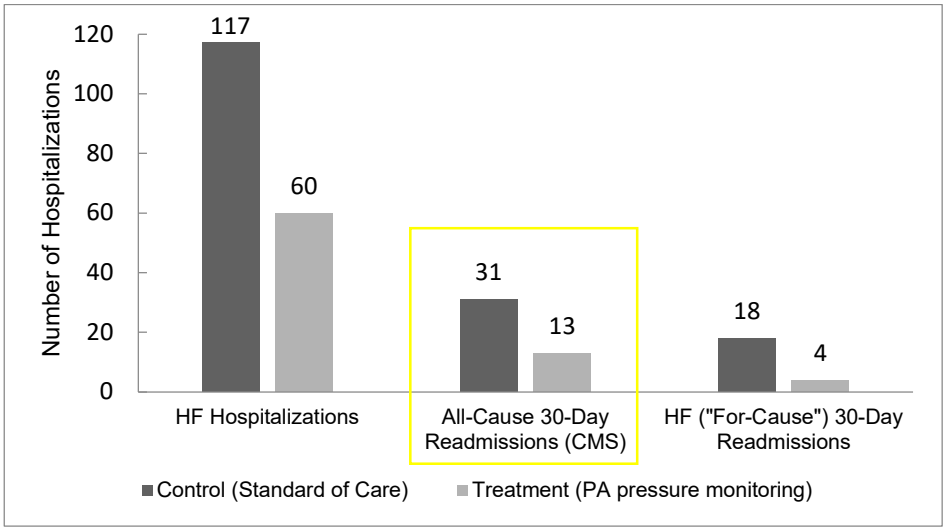
broader range of patients, including those with mild to moderate heart failure and those with elevated natriuretic peptides and no previous heart failure hospitalizations.[12]

In the **CHAMPION** clinical trial, 245 patients (45%) were 65 years or older at the time of sensor implantation (120 in the Treatment group and 125 in the Control group). Patients who were in the Treatment group and managed on the basis of PA pressure information obtained from the CardioMEMS HF System had a significantly reduced HF hospitalization rate (0.34 events/patient-year) compared to patients who were in the Control group (0.67 events/patient-year) and managed according to best available practices (HR 0.51, 95% CI 0.37 – 0.70, p < 0.0001).[11]

The cumulative number of HF hospitalizations in the treatment group of the CHAMPION Clinical Trial was reduced by 49%, relative to the control group.[67] While a valuable metric on its own, investigators of the CardioMEMS HF System sought to re-create more specifically the National Quality Forum (NQF) metric adopted by CMS related to 30-day, all-cause readmission to an acute-care facility, now and a basis for the U.S. Medicare Hospital Readmissions Reduction Program.[67] Based on the major programmatic criteria utilized by CMS (e.g., 65 years old, index admission with primary diagnosis of HF, 30-day readmission), patients in the Treatment group experienced a relative 58% reduction in 30-day, all-cause readmissions versus the control group patients (p = 0.0062) (Figure 7).[67]

Desai et al. conducted a retrospective cohort utilizing U.S. Medicare claims data from 1114 patients undergoing PA pressure sensor implantation between June 1, 2014, and December 31, 2015.[52] Among 1,114 patients receiving implants, there were 1,020 HFHs in the 6 months before, compared with 381 HFHs (HR 0.55, 95% CI 0.49 to 0.61, p < 0.001). These data provide real world evidence supporting the incremental value of this approach to HF management within a Medicare population.

Figure 7. Effect of PA Pressure Monitoring on HF Hospitalizations and All-Cause 30-Day Readmissions Utilizing CMS Criteria



Lastly, Abraham et al. utilized a contemporary propensity matching to study outcomes in matched treatment (n=1087) and control (n=1087) cohorts solely from the U.S. Medicare claims database.[53] Over the 12-month follow-up period the clinical outcomes resulted in a 24% reduction in HF hospitalization rate (p<0.001) and 30% reduction in all cause crude mortality rate (p<0.001) for the treatment group. Moreover, the results indicate that there were 17.5-18.5 fewer days lost to death, HF hospitalization or death, and all cause hospitalization.

CardioMEMS leverages remote monitoring and telehealth to proactively manage heart failure patients. Use of this innovative technology is aligned with the vast expansion of telehealth and digital medicine. This is especially important in removing geographical disparities for all Medicare patients.

Beneficiary access to the CardioMEMS HF System is warranted, through coverage policies and benefit solutions, to enable earlier intervention and management of heart failure before decompensation begins to occur. Doing so, significant improvements in patient care, outcomes and reduced cost may be realized by the community.

The CardioMEMS™ HF System represents a significant and meaningful impact on patients afflicted with NYHA Class II or III heart failure. Level I randomized controlled and other peer-reviewed evidence coupled with long-term outcomes and real-world experience satisfy the fundamental requirement that a technology be deemed reasonable and necessary as a condition of coverage under 1862(a)(1)(A).

5. PROPOSED COVERAGE DETERMINATION: OUTPATIENT WIRELESS PA PRESSURE MONITORING FOR HEART FAILURE

Coverage for wireless hemodynamic monitoring using PA pressure is reasonable and necessary, and will be approved only when an FDA-approved system, such as the CardioMEMS HF System, is used, and all of the following additional safeguards are demonstrated to be in place:

1. Selection of Appropriate Patients:

   Remote implantable hemodynamic monitoring devices for heart failure are covered when the device has received Food and Drug Administration (FDA) Premarket Approval (PMA) for that device's FDA-approved indication and meet all of the following specifications indicated below:

   - NYHA Class II or NYHA Class III heart failure symptoms predominantly present over the previous 30 days despite maximally tolerated guideline-directed medical and device therapies regardless of left ventricular ejection fraction (LVEF);
   - Patients who are able to tolerate dual antiplatelet or anticoagulation therapy for one-month post implant;
   - Patients should be within the anatomical considerations per the manufacturer's IFU for appropriateness of sensor functionality (e.g., body mass index (BMI), chest circumference)[c];
   - At least one heart-failure-related hospitalization within the past 12 months

     OR

     An elevated NT-proBNP or BNP defined per manufacturer's IFU[d].

2. Requirements for Facility and Clinician Education and Training:

   Hospital infrastructure requirements should include:

   - Implanting physician trained to perform right heart catheterization;
   - Cardiac catheterization facility with fluoroscopy equipment and digital angiography capability, as well as the ability to capture and save images;
   - Trained non-physician personnel in the catheterization facility to support the sensor implantation and perform sensor calibration;
   - Trained fluoroscopy technologist needs to be present to support implant procedure to guide sensor placement;
   - At least one hospital interrogation unit dedicated to the implant procedure for sensor calibration post-implantation.

[c] Example from CardioMEMS IFU: Patients with a body mass index (BMI) < 35kg/m2. If BMI is ≥ 35 kg/m2 then, patient should have a chest circumference of < 65 inches

[d] Example from GUIDE-HF:

- Subjects with LVEF ≤40%: NT-proBNP ≥1000 pg/mL (or BNP ≥250 pg/mL)
- Subjects with LVEF >40%: NT-proBNP ≥700 pg/mL (or BNP ≥175 pg/mL)
- Thresholds for NT-proBNP/BNP corrected for BMI using a 4% reduction per BMI unit over 25 kg/m2

Operator requirements should include:

- Implanting physicians with training and facility privileges to perform right heart catheterization and pulmonary angiography;
- Implanting physicians must receive prescribed training by the manufacturer on the safe and effective use of the device per the manufacturer's IFU;
- Physicians or qualified healthcare providers involved in the follow-up of the patients must receive prescribed remote hemodynamic monitoring education per the manufacturer's IFU.

Consistent with FDA-mandated requirements for wireless hemodynamic monitoring using PA pressure, facilities and clinicians must complete the FDA-approved Training Program and all applicable FDA-required Training Modules and requirements prior to qualifying for use of the relevant FDA-approved system for wireless hemodynamic monitoring using PA pressure. An example of a training course can be found in the appendices.

Qualifying facilities and clinicians must document their satisfactory completion of the required Education and Training and, prior to using wireless hemodynamic monitoring using PA pressure, must submit a completed Enrollment Form and sign a Clinic Users Agreement for the relevant FDA-approved system for wireless hemodynamic monitoring using PA pressure.

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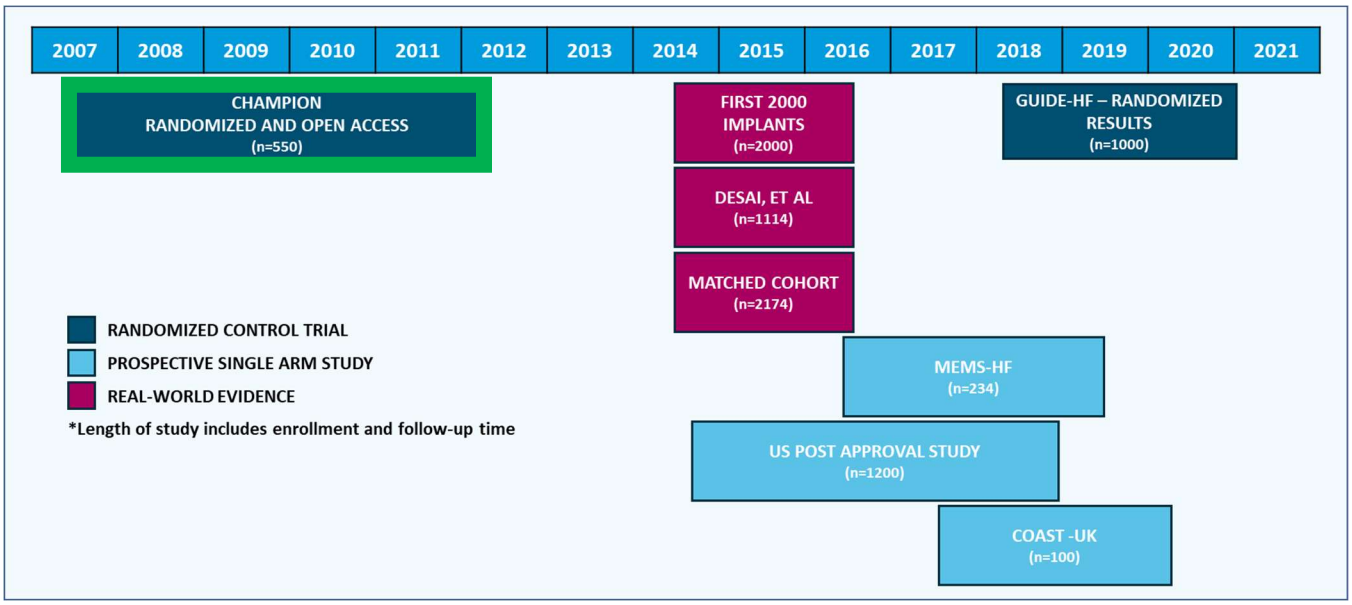
ENCLOSURES/ATTACHMENTS

a. CardioMEMS HF System Guide
b. CardioMEMS HF System User's Manual
c. CardioMEMS Hospital System Guide
d. CardioMEMS HF System Website Guide (Merlin.net™ Patient Care Network: Help Manual)
e. CardioMEMS HF System Training Modules
f. CardioMEMS HF System Integrated Summary of Safety and Effectiveness Data – 2014 Original Indication
g. CardioMEMS HF System Integrated Summary of Safety and Effectiveness Data – 2022 Expanded Indication

APPENDIX

CHAMPION Clinical Trial



Randomized Controlled and Open Access Outcomes: CHAMPION Clinical Trial Results[11,45]

The CHAMPION Clinical Trial was a prospective, multi-center, randomized, single-blind clinical trial in patients with NYHA functional Class III heart failure symptoms regardless of LVEF or aetiology in which all patients were implanted with the sensor and transmitted daily PA pressure readings from home. Subjects (n = 550) were randomized 1:1 and blinded to their assignments at 64 sites located within the U.S. Randomization included subjects to the Treatment group (physician access to PA pressures, n = 270) or the Control group (no physician access to PA pressures, n = 280). All patients received guideline-directed medical therapy (GDMT) in accordance with standard of care HF management practice.

Defined *a priori*, the primary efficacy endpoint of the study was the rate of HF-related hospitalizations at 6 months. Safety endpoints were: (i) freedom from device-related or system-related complications; and (ii) freedom from pressure sensor failures. This trial was registered through ClinicalTrials.gov at NCT00531661.

CHAMPION Major Inclusion Criteria:

- Age greater than 18 years
- Heart failure for at least 3 months, with either preserved or reduced LVEF
- NYHA functional Class III symptoms
- Patients with reduced ejection fraction (< 40%) should be taking a beta blocker for at least 3 months and an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker for at least 1 month, unless the patient cannot tolerate these drugs.
- At least one hospitalization for heart failure within the past 12 months
- Pulmonary artery branch diameter intended for implant should have a diameter between 7 mm and 15 mm
- Patients with a cardiac resynchronization device should be at least 3 months post-implant

CHAMPION Major Exclusion Criteria:

- Active infection
- History of recurrent (> 1) pulmonary embolism or deep vein thrombosis
- Inability to perform right heart catheterization
- Major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of initial assessment
- Glomerular filtration rate < 25 ml/min, unresponsiveness to diuretic therapy, or on chronic renal dialysis
- Congenital heart disease or mechanical right heart valve
- Hypersensitivity or allergy to aspirin and/or clopidogrel

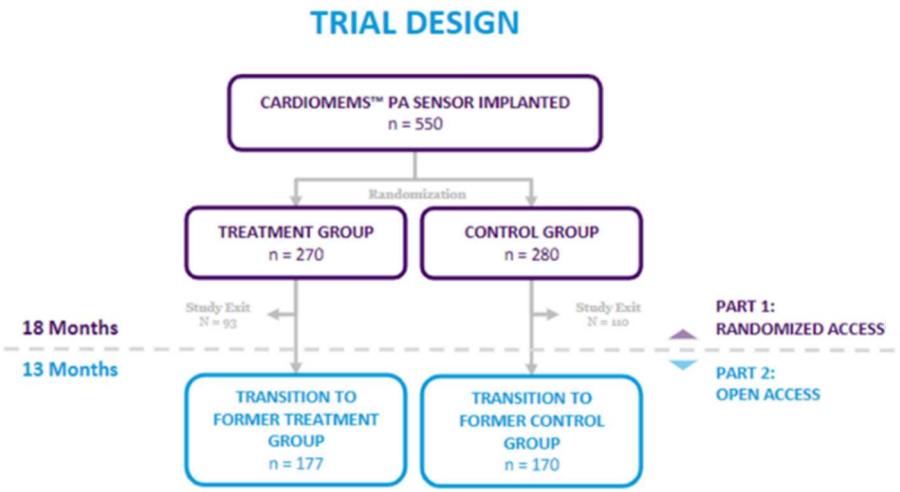
Detailed Methods – CHAMPION Trial Design[11, 49]

The primary safety and efficacy endpoints and all secondary efficacy endpoints were then evaluated. The primary safety endpoints were the rate of device- and system-related complications, and the rate of sensor failures. The primary efficacy endpoint was the rate of HF hospitalizations. Secondary endpoints were tested in a hierarchical fashion and included changes in PA pressures, proportion of subjects hospitalized for HF, days alive outside of the hospital and quality of life. All hospitalizations were adjudicated by members of an independent Clinical Events Committee (CEC) who were blinded to treatment assignment.

The hypothesis tested in the CHAMPION Clinical Trial was that treatment of symptomatic patients with HF based on knowledge of PA pressures would be a superior means to maintain stability and prevent clinical decompensation that leads to hospitalization. This was a single-blinded study, as the physicians caring for the patients had to see the pressures to make treatment decisions. Because blinded follow-up was continued until the last patient completed 6 months of follow-up, pre-specified supplementary analyses were also conducted on the full duration of follow-up data (Randomized Access) to assess the impact of the CardioMEMS HF System on long-term outcomes.

Following the completion of the Randomized Access period, patients transitioned to a period of Open Access during which PA pressures were provided to physicians for patients in both the Treatment and the Control groups. Specifically, physicians continued to have access to the Treatment group's PA pressures in an unchanged manner, whereas access to the Control group's PA pressure was provided for the first time.

Figure 8. CHAMPION Trial Design: Randomized Access and Open Access



Patient Demographics and Disposition

Between September 6, 2007, and October 7, 2009, 575 patients provided informed consent to be involved in the trial and underwent right heart catheterization for device implantation. A total of 550 patients were implanted with the PA pressure sensor and were randomized in the trial. These two groups were well matched with respect to baseline characteristics.

The mean follow-up during the Randomized Access period was 18 months, for a total duration of approximately 800 patient years. During the course of Randomized Access, 93 patients in the Treatment group and 110 patients in the Control group exited the study with the primary reason being death. A total of 347 patients (177 in the Treatment group and 170 in the Control group) completed Randomized Access and entered Open Access. The mean follow-up during Open Access was 13 months for a total duration of approximately 375 patient years. During the course of Open Access, 58 patients in the Treatment group and 43 patients in the Control group exited the study with the primary reason being death.[45]

CHAMPION Results

Safety

The study met the two primary safety endpoints: (i) freedom from device- and system-related complications (DSRC) and (ii) freedom from sensor failure. The protocol's pre-specified objective performance criteria (OPC) were that at least 80% of patients were to be free from DSRC and at least 90% were to be free from pressure sensor failure.

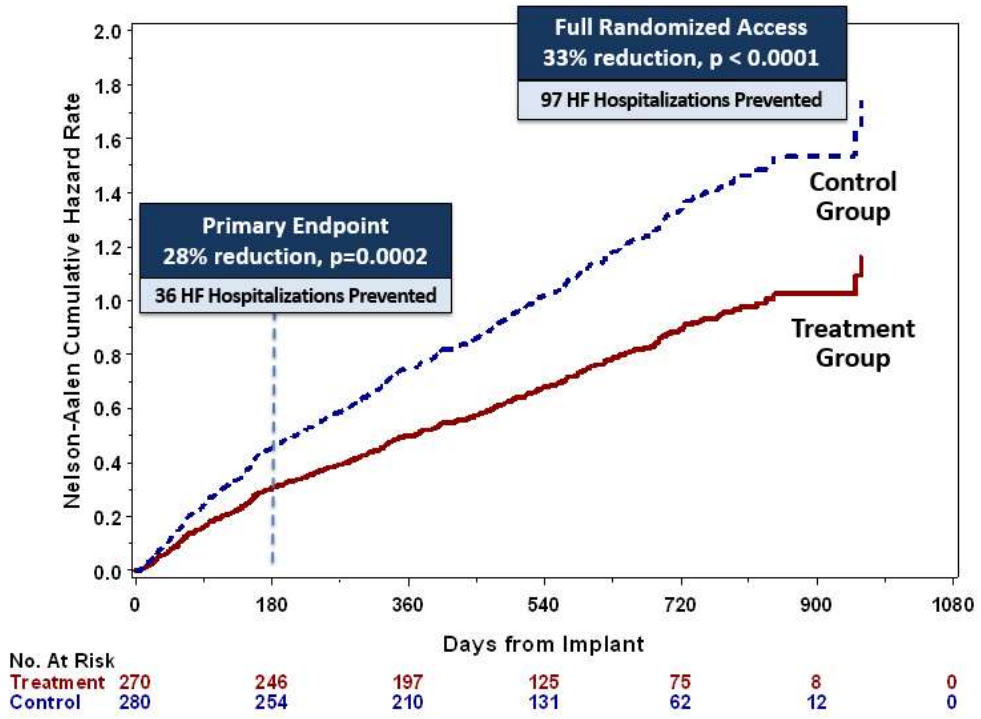
- Of the 575 patients in the safety population, 567 (98.6%) were free from DSRC at 6 months (lower confidence limit 97.3%, $p < 0.0001$). This lower limit of 97.3% is greater than the pre-specified OPC of 80%.[11]
- There were no sensor explants or repeat implants and all sensors were operational at 6 months for a freedom from sensor failure of 100% (lower confidence limit 99.3%, $p < 0.0001$). This lower limit of 99.3% is greater than the pre-specified OPC of 90%.[11]

In addition, no additional DSRC or sensor failures occurred over the entire duration of Randomized Access and Open Access highlighting the excellent safety and performance profile of the CardioMEMS HF System.[45]

Primary Efficacy – Randomized Access

After 6 months of management using the CardioMEMS HF System, the Treatment group experienced a 28% reduction in HF hospitalizations when compared to the Control group. After a mean of 15 months of follow-up, the rate of HF hospitalizations was 37% lower in the Treatment group than in the Control group[19]; by a mean of 18 months of follow-up, this lower rate of HF hospitalizations in the Treatment group was sustained at 33%[45].

Figure 9. **HF Hospitalization Rates Over Randomized Access**



Secondary Efficacy Endpoints - Randomized Access

Changes in PA Pressures

At baseline, both Treatment and Control patients had similar PA mean pressures. The change in pressure over the first 6 months was evaluated by integrating the area under the pressure curve (AUC). At 6 months of follow-up, the Treatment group had a significantly greater reduction in AUC of -156 mmHg days compared to the control group that had an increase in AUC of +33 mmHg days ($p = 0.008$).[11]

Proportion of Subjects Hospitalized for Heart Failure

After 6 months of follow-up, the proportion of subjects hospitalized for one or more HF hospitalizations was significantly lower in the Treatment group (55 out of 270 patients) than in the Control group (80 out of 280 patients) (20% vs. 29%; p = 0.03). [11] After 12 months of follow-up, the proportion of subjects hospitalized for one or more HF hospitalizations was significantly lower in the Treatment group (76 out of 270 patients) than in the Control group (103 out of 280 patients) (28.2% vs. 36.8%; p = 0.0362).[44]

Days Alive Outside of the Hospital (DAOH)

After 6 months of follow-up, Treatment patients had on average 2.3 more DAOH compared to Control patients (174.4 vs. 172.1, p = 0.03)[11]. DAOH was also analyzed after 12 months of follow-up. For patients in the Treatment group being managed using the CardioMEMS HF System, Treatment patients experienced 6.1 more DAOH than Control patients after 12 months of follow-up (313.7 vs. 307.6, p = 0.0219).[44]

Quality of Life

Heart failure specific quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire total score at 6 months. Lower scores are associated with a better quality of life compared to higher scores. The average total score in the Treatment group was 45 ± 26, which was significantly better than the average total score in the Control group 51 ± 25 (p = 0.02). Thus, all the secondary efficacy endpoints were met with high statistical and clinical significance demonstrating a robust and consistent benefit for the Treatment group utilizing the CardioMEMS HF System. [11]

Efficacy – Open Access

At the end of the randomized period of the trial (average follow-up of 18 months), each patient that remained in the trial entered Part 2, also known as "Open Access". [45] During this part of the trial, patients formerly in the Control group received hemodynamic guided HF management for the first time, while former treatment patients continued receiving hemodynamic guided care.

Former Control patients had a high, but stable heart failure event rate (0.68 events/patient/year) at an average of 18 months follow-up in the randomized part of the trial. Heart failure hospitalization rates dropped significantly after an average of 13 months of follow-up during the Open Access period of the trial (0.68 events/patient/year Part 1 vs. 0.38 events/patient/year Part 2, p<0.0001, NNT=3).

Table 8. HF Hospitalization Rates in the Control Group in the Transition from Randomized to Open Access

	HF Hospitalization Rate (events/patient year)	Hazard Ratio (95% CI) p value
Former Control (Open Access)	0.36	0.52 (0.40-0.69) p<0.0001
Control (Randomized Access)	0.68	

Results from Andersen-Gill model with frailty - Hazard Ratio (HR) and 95% Confidence Interval (CI)

Additionally, the low event rate in the Treatment group continued during the Open Access period (0.48 events/patient/year Part 1 vs. 0.45 events/patient/year, p=0.58).

Table 9. HF Hospitalization Rates in the Treatment Group in the Transition from Randomized to Open Access

	HF Hospitalization Rate (events/patient year)	Hazard Ratio (95% CI) p value
Former Treatment (Open Access)	0.45	0.93 (0.70-1.22) p=0.5838
Treatment (Randomized Access)	0.48	

Results from Andersen-Gill model with frailty - Hazard Ratio (HR) and 95% Confidence Interval (CI)

These findings are important because the Open Access period was not influenced by trial design, sponsor interactions or any other potential source of bias that may influence efficacy estimates. The fact that hospitalization rates were reduced in a similar manner in Former Control patients as they transitioned into Open Access reinforced the efficacy findings of the entire trial. Furthermore, the impact of hemodynamic guided heart failure management was now proven to have significant durability with clinical trial testing over an average of 31 months.[45]

The CardioMEMS HF System Impact on Mortality Resulting from Heart Failure

At 18 months average follow up time in the Randomized Access period, the treatment group had a trend towards reduced mortality (HR 0.80, 95% CI 0.55 – 1.15, p=0.23). During the Open Access Period the former control group also showed a trend towards reduced mortality when compared to the mortality rate of the control group during the Randomized Access Period (HR 0.71, 95% CI 0.43 – 1.17, p=0.17)

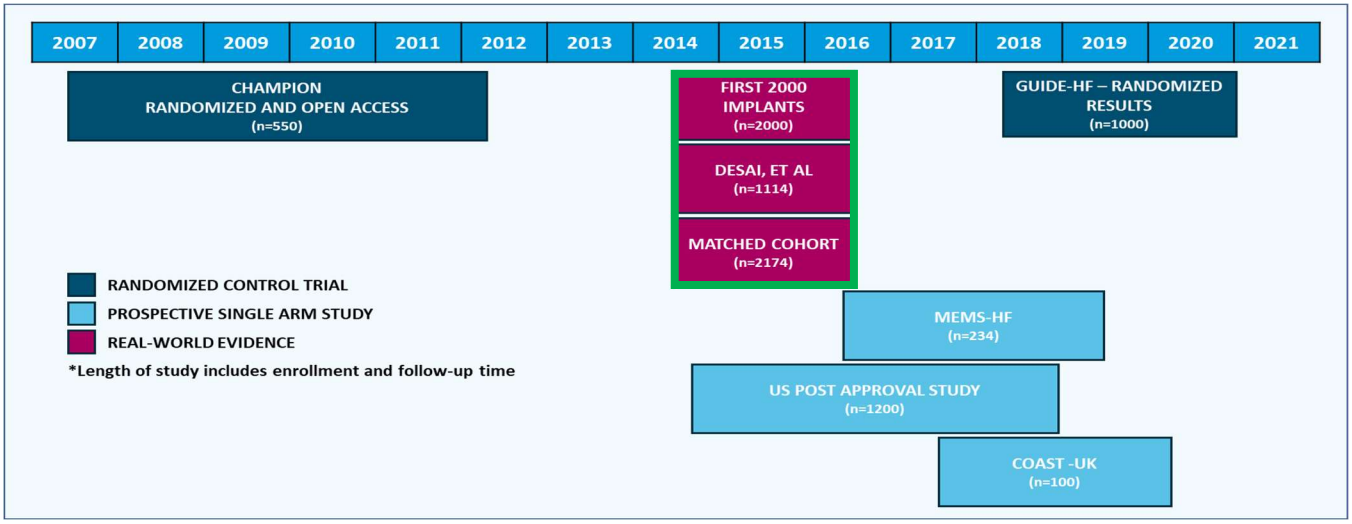
In a subgroup analysis of the 456 patients enrolled in CHAMPION with HFrEF, there was a strong trend for 32% lower mortality (HR: 0.68; 95% CI: 0.45 - 1.02; p=0.06). Compared with controls, patients receiving both components of optimal GDMT (defined as a combination of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) with beta-blockers (BBs) (n=337) had 43% lower HF hospitalizations (HR: 0.57; 95% CI: 0.45 to 0.74; p<0.0001) and 57% lower mortality (HR: 0.43; 95% CI: 0.24 to 0.76; p=0.0026).[50]

CHAMPION SUMMARY

The CHAMPION Clinical Trial achieved all pre-specified primary efficacy and safety endpoints, as well as all pre-specified secondary endpoints. All secondary efficacy endpoints were positive and favored the treatment group. The CHAMPION IDE pivotal trial resulted in both CE Mark and FDA approval because the clinical evidence demonstrated the efficacy and safety of PA pressure monitoring to treat HF patients and reduce HF hospitalizations. Patients whose HF treatment decisions were based on hemodynamic monitoring data obtained from the CardioMEMS HF System experienced a statistically significant 28% relative risk reduction in HF-related hospitalizations as compared with control group patients at 6 months, and had a 33% reduction in HF-related hospitalizations over the study duration (average follow-up 18 ± 7 months).[44]

The CHAMPION trial randomized and open access periods represent one of the longest follow-up trials assessing diagnostically guided heart failure care. This study examined the efficacy of hemodynamic guided heart failure medical management of previously hospitalised NYHA Class III heart failure patients over 31 months of follow-up. The reduction in the need for admission to hospital, both all-cause and heart failure related, seen during the first 6 months was maintained during longer randomized access follow-up and subsequently during open access in which adjustment of therapy was no longer monitored by study staff protocol. The totality of evidence supports the concept that PA pressure-guided heart failure management is superior to clinical assessment alone in heart failure patients with persistent symptoms following admission to hospital.

REAL WORLD STUDIES



FIRST 2000 COMMERCIAL IMPLANTS HEYWOOD ET AL.[51]

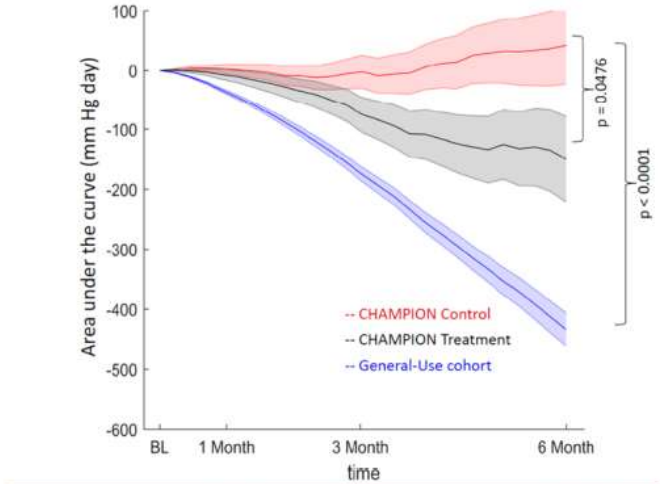
An analysis of PA pressure trends and transmission adherence was performed in the first 2000 patients after commercialization with at least 6 months of follow-up data by Heywood et al. Changes in PA pressures were evaluated using area under the curve (AUC) methodology to estimate the total increase or decrease in pressures during the 6-month follow up period relative to the baseline values. In addition, patients were followed to see if they would adhere to their data transmissions.

RESULTS

Patients with hemodynamic guided care had an AUC of -32.8 mmHg days at the 1 month, -156.2 mmHg days at the 3 months and -434.0 mmHg days after 6 months, which was significantly lower than the treatment group in the CHAMPION trial. Patients with highest baseline pressure had greatest reduction. HFpEF benefits were equal to HFrEF patients.

Patient compliance remained consistent with 1.27 days between data transmissions at 6-months. The results of this study demonstrated that there is a significant reduction in PA pressures in a real-world practice.

Figure 10. Mean PA pressure trends in patients seen in CHAMPION and the General-Use Cohort



CHAMPION Control	(275pts)	3.1 ± 6.7 (270pts)	-5.5 ± 24.7 (251pts)	42.0 ± 65.0 (228pts)
CHAMPION Treatment	(270pts)	-7.0 ± 7.7 (266pts)	-59.3 ± 27.6 (257pts)	-150.1 ± 71.0 (236pts)
General-Use cohort	(2000pts)	-32.8 ± 2.9 (1920pts)	-156.2 ± 10.6 (1816pts)	-434.0 ± 27.5 (1655pts)

CONCLUSION

This study provides very important analyses demonstrating that hemodynamic-guided HF management with an implanted PA sensor is generalizable to the normal clinical management of patients with symptomatic HF. Long-term patient acceptance and adherence are clearly demonstrated by an average of 1.2 days between remote pressure transmissions and >98% weekly use of the system. The goal of remote PA pressure monitoring is to incorporate the pressure information in decision making leading to medical intervention expressly to lower pressures. The current data, in the first consecutive 2000 patients managed with PA pressure information for at least 6 months, demonstrate that pressures were significantly lower compared with baseline.

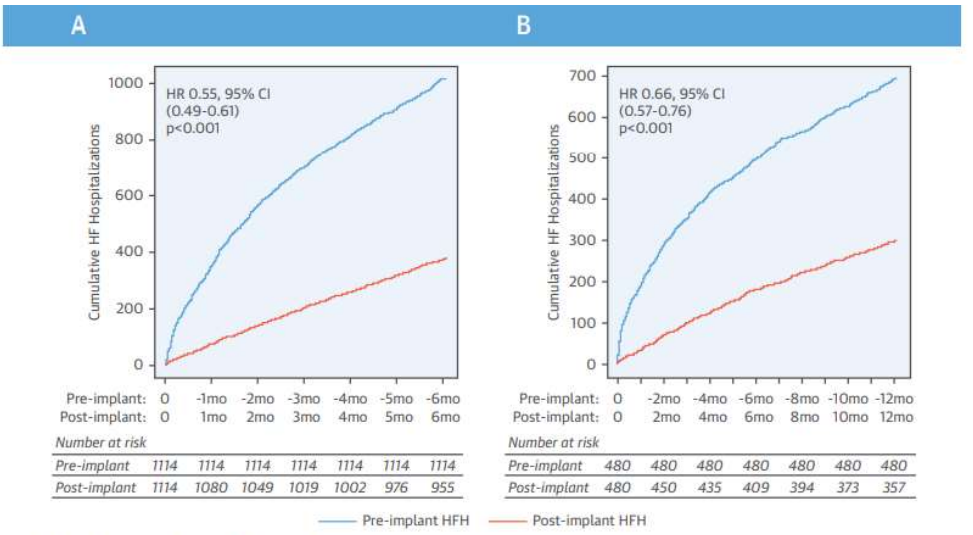
DESAI ET AL.[52]

The real-world clinical efficacy and cost-effectiveness of hemodynamic monitoring with the CardioMEMS™ System was studied by Desai et al. A retrospective cohort was identified using CMS administrative claims data from the Standard Analytic File to evaluate health care utilization in 1114 U.S. fee-for-service Medicare beneficiaries receiving a PAP sensor implant during the period following FDA approval for commercial use.

RESULTS

In the 6-months before implantation, the 1114 patients had 1020 HF hospitalizations, and in the 6-months following CardioMEMS™ implant there were 381 hospitalizations. The significant reduction in hospitalization frequency was sustained to 1-year after CardioMEMS™ implant.

Figure 11. Cumulative HFHs During the Period Before and After PA Pressure Sensor Implantation



Desai, A.S. et al. J Am Coll Cardiol. 2017;69(19):2357-65.

(A) 6-month cohort. **(B)** 12-month cohort. Hazard ratios were derived using the Andersen-Gill extension of the Cox proportional hazards model, accounting for the competing risk of death, ventricular assist device, or transplant. Note that event accumulation during the pre-implant interval is counted backward from the time of implant. Data highlight significant reductions in cumulative HFHs in the period after device implantation compared with the period before implantation for both the 6- and 12-month cohorts. CI = confidence interval; HF = heart failure; HFH = heart failure hospitalization; HR = hazard ratio.

Reductions in HFH were associated with an estimated reduction in costs related to HF care of $7,433/ patient in the 6 months following implantation relative to the period before implantation (IQR: $7,000 to $7,884/patient at 6 months before implantation; $p < 0.001$). The reductions in health care utilization in the post-implant period translated into substantial cost reductions at both 6-months and at 1-year compared to the pre-implant time.

CONCLUSION

These data provide real-world evidence supporting the incremental value of this approach to HF management. The observation of sustained cost reductions out to one year in a real- world population supports the concept that the benefits of hemodynamic monitoring are durable over longer term follow up, a factor that is essential for long-term cost-effectiveness.

PROPENSITY MATCHED COHORT ANALYSIS ABRAHAM ET AL.[53]

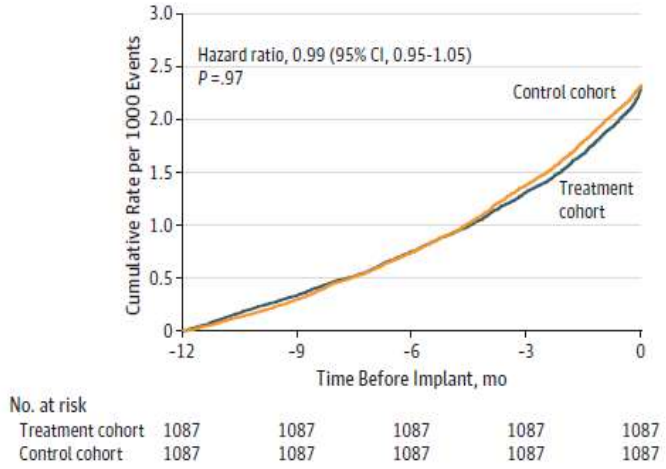
To further examine the impact of ambulatory hemodynamic monitoring on clinical outcomes in patients with heart failure we can look to the retrospective cohort study conducted by Abraham, et al (2019).[81] This study utilized a matching procedure to study outcomes in matched treatment and control cohorts solely from the U.S. Medicare claims database.

As previously mentioned, all the patients involved in the study were Medicare beneficiaries. The total number of patients that had received a CardioMEMS™ system (N=1087) were matched to a cohort of control patients (N=1087) that did not receive a CardioMEMS™ sensor based on preimplant demographic features such as history

of heart failure and number of hospitalizations. The matching was conducted through various iterative searches through the same database to locate the patients with similar demographic attributes.

Initially when comparing the treatment arm (CardioMEMS™ implant) to the control arm (no implant) both groups of patients had no differences in baseline characteristics. The figures below highlight how closely the two cohorts matched.

Figure 12. Similarity between the Treatment Group and Control Group in the Propensity Matched Cohort Analysis



Characteristic	Cohort, No. (%) Treatment (n = 1087)	Control (n = 1087)	P Value
Demographic factors			
Age, median (IQR), y	73 (67-80)	74 (67-80)	.60[a]
Female	381 (35.1)	381 (35.1)	>.99
Race/ethnicity			
White	910 (83.7)	910 (83.7)	>.99
Black	137 (12.6)	137 (12.6)	>.99
Hispanic	11 (1.0)	11 (1.0)	>.99
Asian	13 (1.2)	13 (1.2)	>.99
Other	16 (1.5)	16 (1.5)	>.99
History of ICD or CRT device	494 (45.4)	494 (45.4)	>.99
Comorbidities			
Arrhythmia	810 (74.5)	824 (75.8)	.52
Hypertension	945 (86.9)	963 (88.6)	.27
Diabetes	577 (53.1)	564 (51.9)	.61
Pulmonary disease	608 (55.9)	638 (58.7)	.21
Renal disease	540 (49.7)	580 (53.4)	.09
Without end-stage renal disease	1068 (98.3)	1068 (98.3)	>.99

RESULTS

Over the 12-month follow-up period the clinical outcomes resulted in a 24% reduction in HF hospitalization rate (P<0.001) and 30% reduction in all cause crude mortality rate (P<0.001) for the treatment group. Moreover, the results indicate that there were 17.5-18.5 fewer days lost to death, HF hospitalization or death, and all cause hospitalization.

Figure 13. Clinical Results from the Propensity Matched Cohort Analysis

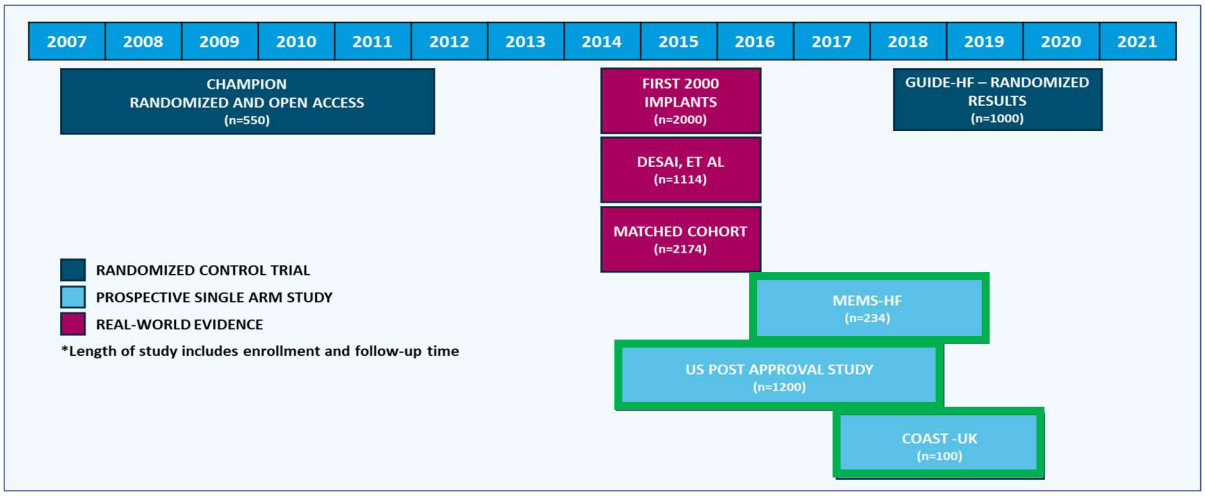
Outcome	Patients, No. (%) Treatment Cohort (n = 1087)	Control Cohort (n = 1087)
Clinical events		
Heart failure hospitalization, No. of events[a]	616	784
Death	241 (22.2)	325 (29.9)
Ventricular assist device or transplant	20 (1.8)	13 (1.2)
Hospitalization for any cause, No. of events	1846	1818
Patients with ≥1 clinical event		
Heart failure hospitalization[a]	345 (31.7)	422 (38.8)
Heart failure hospitalization or death[a]	469 (43.1)	597 (54.9)
Hospitalization for any cause	695 (63.9)	695 (63.9)
Hospitalization for any cause or death	735 (67.6)	783 (72.0)

Outcome	Mean (SD) Treatment Cohort (n = 1087)	Control Cohort (n = 1087)	Hazard Ratio[a] or Risk Ratio[b] (95% CI)	Absolute Difference, d	P Value
Clinical event rates per patient per y					
Heart failure hospitalization[c]	0.65	0.88	0.76 (0.65-0.89)	NA	<.001
Mortality, death per y	0.23	0.30	0.70 (0.59-0.83)	NA	<.001
Heart failure or death	0.90	1.23	0.73 (0.64-0.84)	NA	<.001
Days lost per patient[a]					
To death	46.2	64.2	0.72 (0.62-0.84)	−17.9	<.001
To heart failure hospitalization or death	50.0	68.4	0.73 (0.63-0.85)	−18.5	<.001
To any-cause hospitalization or death	56.9	74.5	0.77 (0.68-0.88)	−17.5	<.001

CONCLUSION

The findings in this large retrospective study are consistent with results of other studies. HF patients implanted with a CardioMEMS™ HF System had lower rates of mortality and HF Hospitalization at 12 months than their matched control cohort, conveying the use of hemodynamic monitoring improves HF outcomes.

PROSPECTIVE SINGLE ARM STUDIES



MEMS HF

The MEMS-HF prospective study further corroborated previous real-world findings of reduction in PA pressures, HFH, and improved patient-reported quality of life.[54] This trial was conducted amongst patients in regions of The Netherland, Germany, and Ireland aiming to prove the same results as seen previously in US based studies.[83] This was a prospective, single-arm, multi-center, open -label trial consisting of a total of 234 NYHA Class III patients. The objective of this study was to evaluate the safety and efficacy of the CardioMEMS™ HF System in Europe.

The 243 patients were enrolled in 31 centers across Germany, The Netherlands, and Ireland between May 13th, 2016, and March 29th, 2018. Of the total 234 patients, 180 completed follow-ups at 12-months post implant. The two co-primary endpoints were freedom from device/system related complications (80% goal) and freedom from sensor failure (90% goal). Additional endpoints included HF hospitalizations after one-year post implant vs. prior year to implant and survival at 1 year.

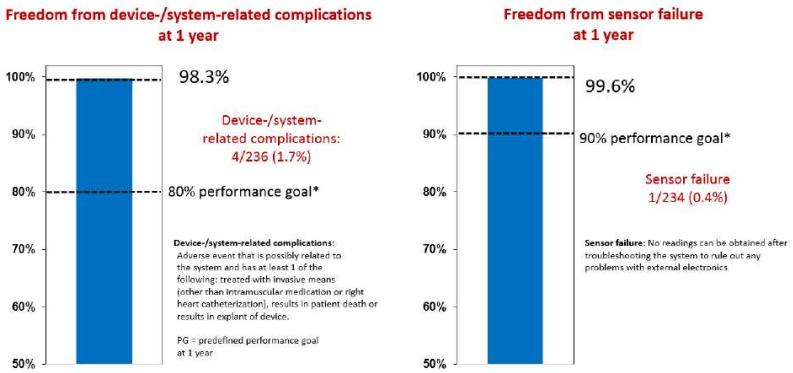
A few key patient characteristics to keep in mind specifically for the MEMS-HF study was that the patient cohort was more acute in terms of being elderly, primarily male, and 75% of the patients had experienced a HF hospitalization within the past 3 months. In addition, baseline PRO assessments indicated impaired health status and depression.

RESULTS

Safety

In this prospective single-arm analysis, both co-primary safety endpoints were met. The goal for freedom from device/system related complications achieved 98.3%; and freedom from sensor failure achieved 99.6%. The figure below indicates how the two safety endpoints exceeded their original goals.

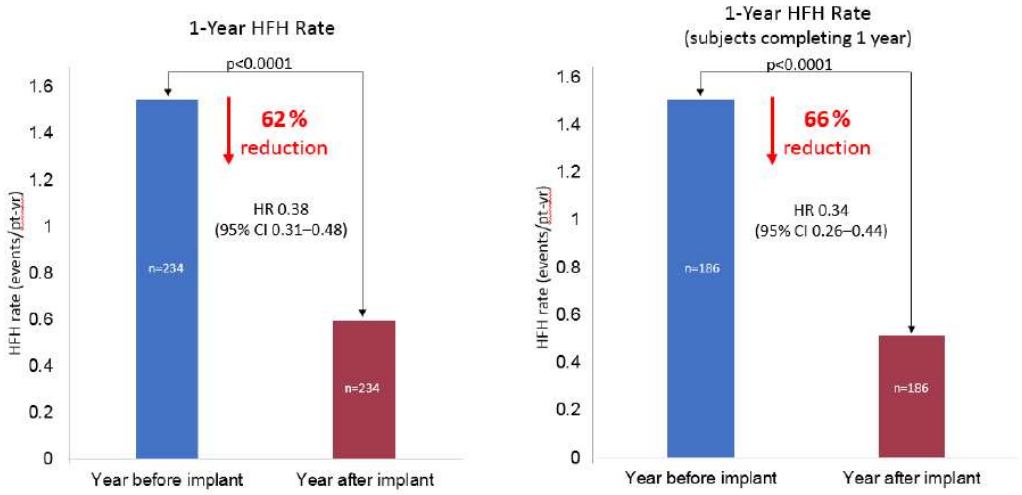
Figure 14. Safety Endpoints from MEMS-HF



Secondary Efficacy Endpoint

The secondary outcomes related to hospitalizations and survival showed an overall reduction of 62% in HFH for all treated patients and 66% reduction in HFH 1-year post-implant compared to 1-year pre-implant for all patients completing the 12-month follow-up.

Figure 15. 1-Year HFH Rate for all Subjects and 1-Year HFH Rate for Subjects who Completed the 12-Month Follow-up



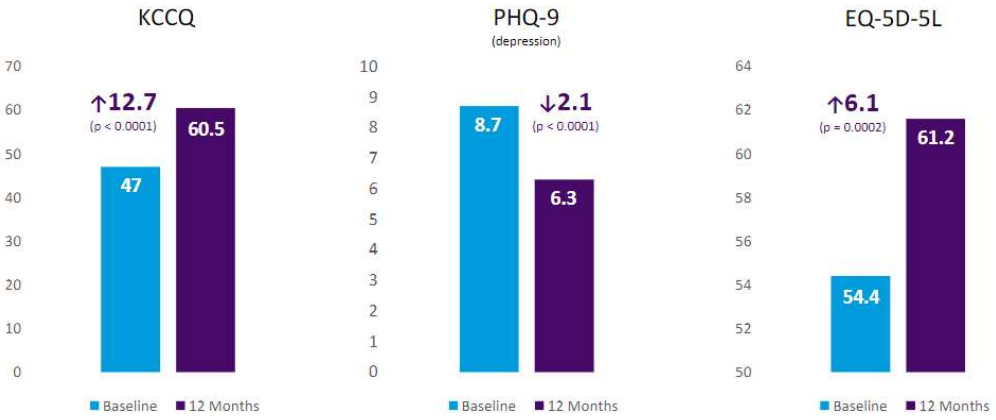
Area Under the Curve

Similar to outcomes of other CardioMEMS™ studies, the results of the study confirmed an overall reduction in PA pressures from baseline at year, and patients with the highest baseline PA pressures had the greatest reduction.

Quality of Life

The metrics included improved patient-reported outcomes related to KCCQ (QoL), PHQ-9 (depression), EQ-5D-5L VAS (QoL) compared to baseline measurements.

Figure 16. Quality of Life Measurements from MEMS-HF



CONCLUSION

The CardioMEMS™ HF system proved to be a safe and reliable tool to help patients treat and reduce PA pressures over time as confirmed in U.S. studies. Like the U.S., favorable clinical outcomes proved to be true in the health systems of Germany, Ireland, and The Netherlands including reduced PA pressure, fewer HF hospitalizations, high survival and an added metric of improved quality of life and fewer depressive symptoms.

CARDIOMEMS US POST APPROVAL STUDY (PAS)

As a condition of approval, the FDA required a post market surveillance study (ClinicalTrials.gov identifier NCT 02279888). The objective of this study was to assess the efficacy and safety of PA pressure-guided therapy in routine clinical practice with special focus on subgroups defined by sex, race, and ejection fraction. This multi-center, prospective, open-label, observational, single-arm trial of 1200 patients across 104 centers within the United States with NYHA Class III HF and a prior HFH within 12 months evaluated patients undergoing PA pressure sensor implantation between September 1, 2014, and October 11, 2017. [55]

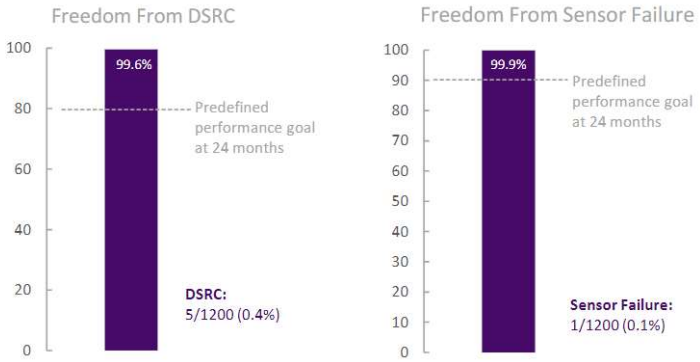
The primary efficacy outcome was the difference between rates of adjudicated HFH 1 year after compared with the 1 year before sensor implantation. Safety end points were freedom from device- or system-related complications (DSRCs) at 2 years and freedom from pressure sensor failure at 2 years.

RESULTS

Safety

Although the safety endpoints were set to be evaluated at the year two follow-up mark, already at year one, there were exceeding results for both safety criteria endpoints. These results furthered the clinical results of the CHAMPION Trial and expanded upon its safety data with a large sample size.

Figure 17. Safety Endpoints from PAS

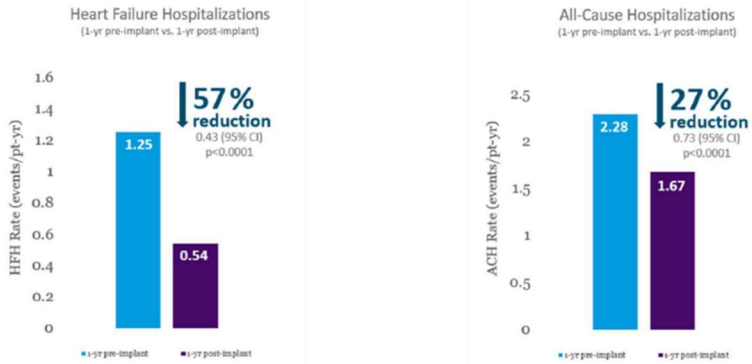


Primary Efficacy Endpoint

Heart Failure Hospitalizations

The PAS demonstrated a 57% HF hospitalizations risk reduction 1-year post-implant compared to 1-year pre-implant (0.54 versus 1.25 events/patient-years, HR 0.43, 95% CI 0.39–0.47, p<0.0001). In addition, all-cause hospitalizations were also reduced following sensor implantation (1.67 versus 2.28 events/patient-years, HR 0.73 95% CI 0.68–0.78, p<0.0001). Results were consistent across subgroups defined by ejection fraction, sex, race, cause of cardiomyopathy, presence/absence of implantable cardiac defibrillator or cardiac resynchronization therapy and ejection fraction.

Figure 18. HF Hospitalization Reduction and All-Cause Hospitalization Reduction



Area Under the Curve

For the entire cohort of patients, PA pressures declined significantly from baseline during the 1 year of observation (AUC, −790.9±2097.0 mm Hg days). The magnitude of decrease in PA pressures was related to baseline PA pressures, with greatest reductions in those with the highest pressures at baseline.

CONCLUSION

The evidence confirmed in the U.S. PAS continues to further support the findings that CardioMEMS™ promotes reduced HFH and PA pressure reductions across a larger cohort. The U.S. PAS data also is a significant driver in proving safety outcomes with over 1,900 patients showing a greater than 98% freedom from DSRC. The frequent transmission activity also provides a secondary benefit of continued patient engagement with healthcare providers.

COAST UK

The CardioMEMS HF System Post-Market Study (COAST) was designed to evaluate the safety, effectiveness, and feasibility of haemodynamic-guided heart failure (HF) management using a small sensor implanted in the PA of New York Heart Association (NYHA) Class III HF patients in the UK, Europe, and Australia. COAST is a prospective, international, multicenter, open-label clinical study (NCT02954341).

The primary clinical endpoint compares annualized HF hospitalization rates after 1 year of haemodynamic-guided management vs. the year prior to sensor implantation in patients with NYHA Class III symptoms and a previous HF hospitalization. The primary safety endpoints assess freedom from device/system-related complications and pressure sensor failure after 2 years. Results from the first 100 patients implanted at 14 out of the 15 participating centers in the UK are reported here.[70]

RESULTS

Safety

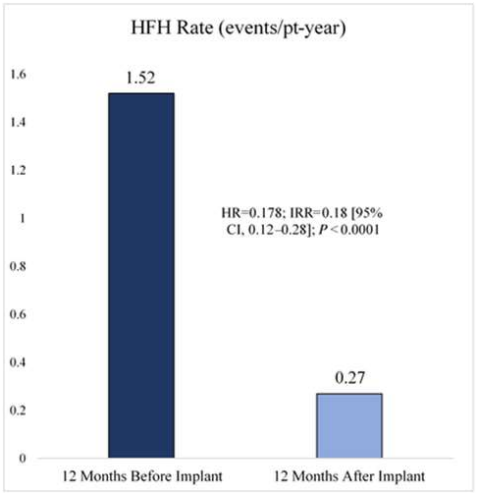
The primary safety endpoints of freedom from DSRCs and freedom from pressure sensor failure at 2 years were 100% and 99% with a lower limit of their confidence interval (96.5%, P<0.0001 and 94.6%, P=0.0006, respectively) exceeding the pre-specified performance goals of 80% and 90%, respectively.

Primary Efficacy Endpoint

Heart Failure Hospitalization

The rate of HFH after 1 year after implant was lower in the cohort compared with the year prior to implant. There were 165 HFH (1.52 events/patient-year) before implant compared with 27 HFH (0.27 events/patient-year) after implant resulting in a significant risk reduction of 82% (IRR 0.18 [95% confidence interval—CI 0.12–0.28]; P < 0.0001)

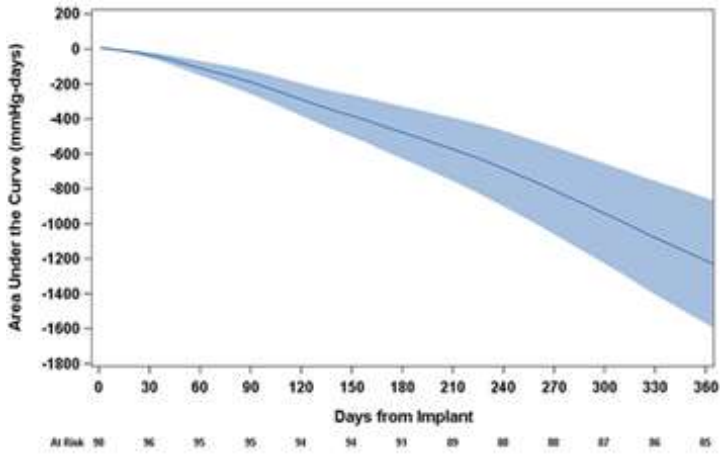
Figure 19. HF Hospitalization Reduction Prior to and After Implant



Area Under the Curve

During the first year of follow-up, PA pressures decreased significantly from baseline. The area under the curve (mmHg-day) reduction at 1 year was significant for all three PA pressure parameters (-1437.3 ± 2300.6 systolic; -936.1 ± 1269.6 diastolic; and -1132.7 ± 1576.0 mm Hg-days, mean; P < 0.0001 for all)

Figure 20. PA Pressure Area Under the Curve Over Time



Patient Experience

Quality of Life

The five different components of the patient's QoL questionnaire and the QoL index were stable throughout the study duration; a paired analysis performed for the mean visual analogue scale score component of the QoL assessment showed an improvement at 12 months with a 2.0 ± 18.6 positive change compared with baseline, although not statistically significant (P = 0.1933)

Functional Class

Functional class improved during study follow-up with 43% of subjects improving from NYHA Class III to NYHA Classes I and II after 12 months.

CONCLUSION

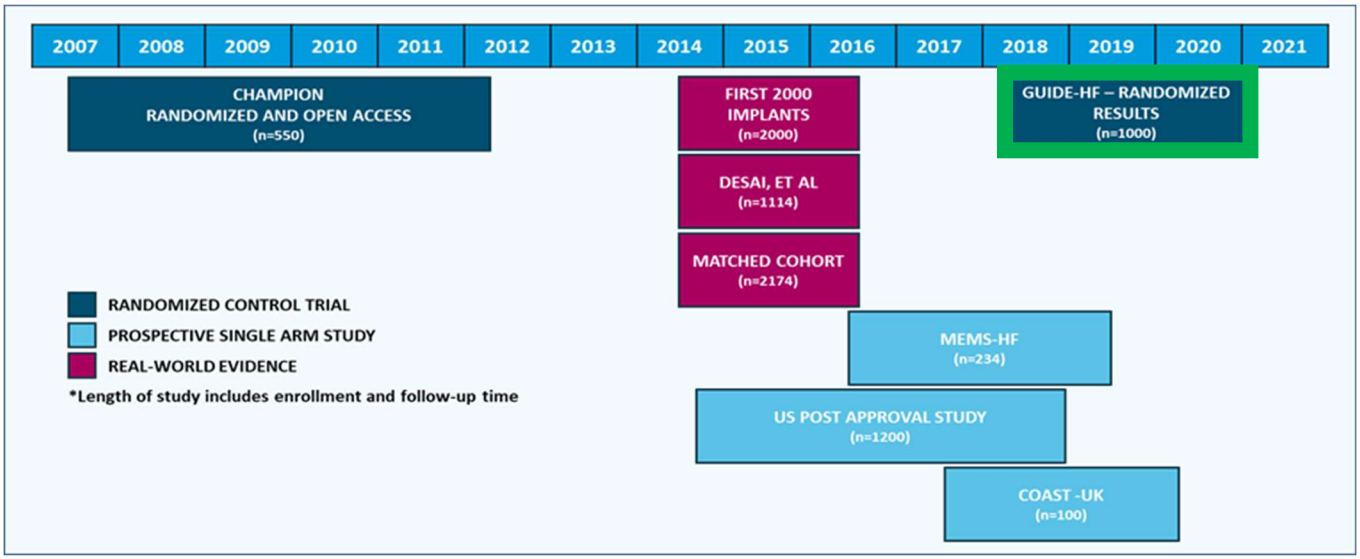
The results reported here are entirely consistent with those in other large studies with similar design and support the usefulness of PA pressure monitoring as a management strategy superior to usual clinical care. The COAST-UK demonstrates that PA pressure-guided therapy is safe and feasible, with a high likelihood of achieving meaningful clinical benefits, in the UK National Health Service system. The clinical benefit of this management strategy extends to patients with HF regardless of ejection fraction. Remote PA pressure monitoring is an opportunity to intensify and improve HF management and outcome in an era that heavily relies on virtual and remote encounters.

CONSISTENT TREATMENT BENEFIT UNDER ORIGINAL INDICATION

Implantable hemodynamic monitoring has emerged as an effective strategy for reducing HF events in patients with NYHA Class III HF symptoms with a prior HFH within 12 months. Consistent benefit has been demonstrated in several retrospective studies from the CHAMPION Trial.[56-59] as well as extensive analysis of "real-world" experience.[51,60] and in Medicare claims data managed in a commercial setting.[52,61]

Whether the benefits of PA pressure guided therapy could be extended to a broader pool of patients with milder (NYHA Class II) or more severe (NYHA Class IV) HF or to those without recent hospitalization for HF but with elevation in natriuretic peptide levels remained unclear. In addition, the potential favorable impact of PA sensor-guided HF management on mortality in patients with NYHA class II-IV HF remained to be understood.

GUIDE-HF CLINICAL TRIAL: RANDOMIZED RESULTS



The GUIDE-HF trial was designed to test the hypothesis that medical intervention intended to lower PA pressures and maintain hemodynamic stability will improve mortality and HFH in patients with NYHA class II-IV symptoms at persistently high risk for poor outcome through a history of previous HFH or elevated natriuretic peptide.[12,48]

Methodology

The randomized arm of the haemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial was a multicenter, single-blind study at 118 centers in the USA and Canada. Following successful implantation of a PA pressure sensor and 1:1 randomization, patients with all ejection fractions, NYHA functional class II–IV chronic heart failure, and either a recent heart failure hospitalisation or elevated natriuretic peptides (based on a-priori thresholds) were treated either with standard-of-care heart failure management using guideline-recommended medical therapy (control group, N=503) or hemodynamic-guided care in addition to guideline recommended medical therapy (treatment group, N=497). Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to PA pressure data for control patients.

The primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalizations and urgent heart failure hospital visits) at 12 months assessed in all randomly assigned patients. Secondary effectiveness endpoints were cumulative heart failure events at 12 months post-implantation, health status at 6 months and 12 months, as assessed by the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12), functional status at 6 months and 12 months assessed by the 6-min hall walk (6MHW) test, and individual components of the primary endpoint at 12 months. Freedom from device-related or system-related complications at 12 months was the safety endpoint. A pre-COVID-19 impact analysis for the primary and secondary outcomes was prespecified. This study is registered with ClinicalTrials.gov, NCT03387813.

GUIDE-HF Major Inclusion Criteria:

- Diagnosis and treatment for HF (regardless of LVEF) for >90 d prior to the date of consent, and on stable, optimally titrated GDMT for at least 30 days
- NYHA Class II, III, or IV HF symptoms documented within 30 days prior to consent
- HFH within 12 m prior to consent and/or elevated NT-proBNP (or BNP) within 30 d prior to consent defined as:
    - Subjects with LVEF ≤40%: NT-proBNP ≥1000 pg/mL (or BNP 250 pg/mL)
    - Subjects with LVEF >40%: NT-proBNP ≥700 pg/mL (or BNP ≥175 pg/mL)
    - Thresholds for NT-proBNP/BNP corrected for BMI using a 4% reduction per BMI unit over 25 kg/m2
- Subjects ≥18 y of age able and willing to provide informed consent
- Chest circumference of <65 in if BMI is ≥35 kg/m^2

- Willing and able to upload PA pressure information and comply with the follow-up requirements

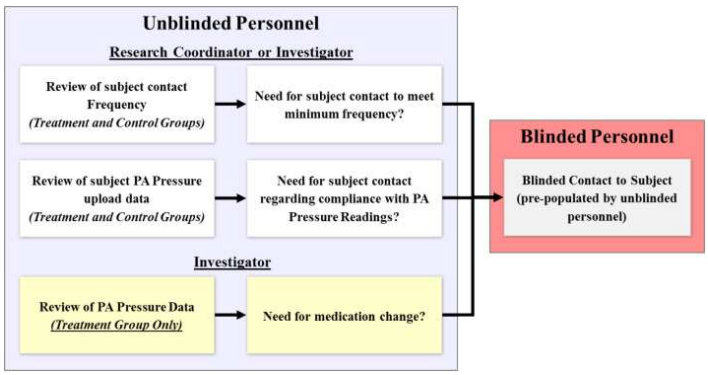
GUIDE-HF Major Exclusion Criteria:

- Intolerance to all neurohormonal antagonists (ie, intolerance to ACE-I, ARB, ARNi, hydralazine/isosorbide dinitrate, and β-blockers)
- ACC/AHA stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
- Received or are likely to receive an advanced therapy (eg, mechanical circulatory support or cardiac transplant) in the next 12 m
- eGFR < 25 mL/min/1.73 m^2 and nonresponsive to diuretic therapy, or receiving chronic dialysis
- Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for 1 m post implantation
- Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS PA Sensor
- Implanted with mechanical right heart valve(s)
- Unrepaired severe valvular disease
- An active, ongoing infection defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum or urine).
- History of current or recurrent (≥2 episodes within 5 y prior to consent) pulmonary emboli and/or deep vein thromboses
- Major cardiovascular event (eg, unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke) within 90 d prior to consent
- Implanted with CRT-P or CRT-D for less than 90 d prior to consent
- Any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (eg, transpulmonary gradient >15) at implant RHC, a history of noncompliance, or any condition that would preclude CardioMEMS PA Sensor implantation

Procedures to Ensure Patient Masking

The GUIDE HF trial was designed with tightly managed nurse communication protocol to ensure masking of the treatment and control arms. Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to PA pressure data for control patients. To maintain patient masking and ensure balanced contact between groups, each site designated masked personnel for all site-to-patient communication related to heart failure management and sites contacted all patients in both treatment groups using a masked caller and scripted language at least once every 2 weeks for the first 3 months, and then once per month until study completion. Clinical symptoms or concerns discovered during the scripted calls were referred to the investigator for management in both treatment and control patients. Standard heart failure management could incorporate typical data including daily weights, symptoms, and other diagnostics from implantable therapy devices, if available. Patient contacts generated by knowledge of PA pressure were communicated to the treatment group through a masked caller using scripted language. All patients were instructed to upload PA pressure data daily. Adherence to daily PA pressure uploads was visible to site staff and monitored for both groups, whereas PA data were only visible to sites for the treatment group. Poor adherence was addressed through a scripted communication by a masked caller reminding patients to upload PA pressure data.

Figure 21. Communication Protocol



Demographics and Baseline Clinical Features

Patient characteristics and medications at baseline were similar between the study groups. Overall, 296 (30%) of 1000 patients from the entire cohort were NYHA functional Class II, 650 (65%) were NYHA functional Class III, and 54 (5%) were NYHA functional Class IV. Enrollment was based on a previous heart failure hospitalisation in 361 (36%) of 1000 patients, on elevated natriuretic peptides alone in 442 (44%) patients, and both in 196 (20%) patients. 74% of patients enrolled were ≥ 65 years of age. Patients with HFpEF made up 47% of the overall cohort.

Table 10. GUIDE-HF Baseline Demographics

	Treatment (N 497)	Control (N 503)
Age - yr	69.2 ± 11.1 (497)	69.2 ± 11.0 (503)
Female Sex	37.6% (187/497)	37.4% (188/503)
LVEF > 40%	45.1% (224/497)	48.7% (245/503)
Race		
White	81.1% (403/497)	80.5% (405/503)
Black	17.5% (87/497)	18.5% (93/503)
Asian	0.0% (0/497)	0.2% (1/503)
American Indian or Alaskan Native	0.4% (2/497)	0.4% (2/503)
Pacific Islanders	0.0% (0/497)	0.0% (0/503)
Other	1.2% (6/497)	0.6% (3/503)
Ethnicity		
Hispanic	3.2% (16/497)	3.4% (17/503)
Non-Hispanic	96.0% (477/497)	96.0% (483/503)
Unknown	0.8% (4/497)	0.6% (3/503)
Body mass index - kg/m^2	32.93 ± 8.33 (497)	33.83 ± 8.43 (503)
NYHA Class		
II	29.4% (146/497)	29.8% (150/503)
III	64.8% (322/497)	65.2% (328/503)
IV	5.8% (29/497)	5.0% (25/503)
Enrollment Type		
HFH in year prior only	34.2% (170/497)	38.0% (191/502)
Elevated NT-proBNP/BNP level in 30 days prior only	46.3% (230/497)	42.2% (212/502)
HFH in year prior and elevated NT-proBNP/BNP level in 30 days prior	19.5% (97/497)	19.7% (99/502)

Between March 15, 2018, and Dec 20, 2019, 1484 patients were screened, of whom 1022 were enrolled, including 1007 patients at 114 sites in the USA and 15 patients at four sites in Canada. 22 patients had unsuccessful implants and were followed up for 30 days for safety outcomes. At trial closure (Jan 8, 2021) fatal and non-fatal outcomes up to 12 months were known for all patients, except for 25 treatment group patients and 44 control group patients who withdrew from the study before 12 months. However, outcomes in these patients were known up to the withdrawal date and included in the endpoint analyses. Time to withdrawal did not differ between the treatment group and control group. As of the US COVID-19 national emergency date of March 13, 2020, 72% of the total follow-up days had been completed.

GUIDE-HF Results

Safety

The safety endpoint (analysis cohort including unsuccessful implants) showed a 99% (1014 of 1022 patients) freedom from device-related or system-related complications.

Table 11. Freedom from Device/System Related Complications over 12 months post-implantation

Analysis Group	Proportion of Subjects without Device or System Related Complication
Treatment (N=497)	99% (494/497)
Control (N=503)	99% (498/503)
Not Randomized (N=22)	100% (22/22)
Safety Population (N=1022)	**99% (1014/1022)**

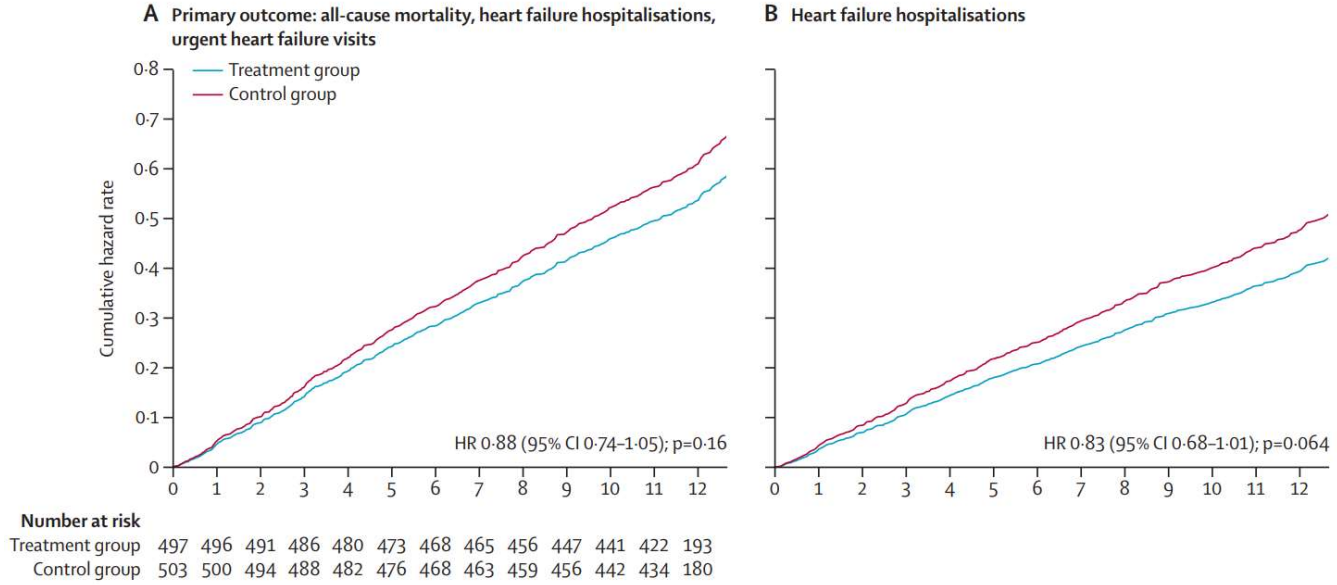
Primary endpoint outcome – Overall Analysis

In the overall analysis, 253 primary endpoint events (0.563 per patient-year) occurred in the treatment group and 289 events (0.640 per patient-year) in the control group (hazard ratio [HR] 0.88, 95% CI 0.74–1.05; p=0.16). There were 185 heart failure hospitalizations in the treatment group and 225 in the control group (HR 0.83, 95% CI 0.68–1.01; p=0.064). There were no significant differences in either urgent heart failure hospital visits or mortality between the treatment and control group in the overall analysis.

Table 12. Primary Endpoint and Component Breakdown for Overall Analysis

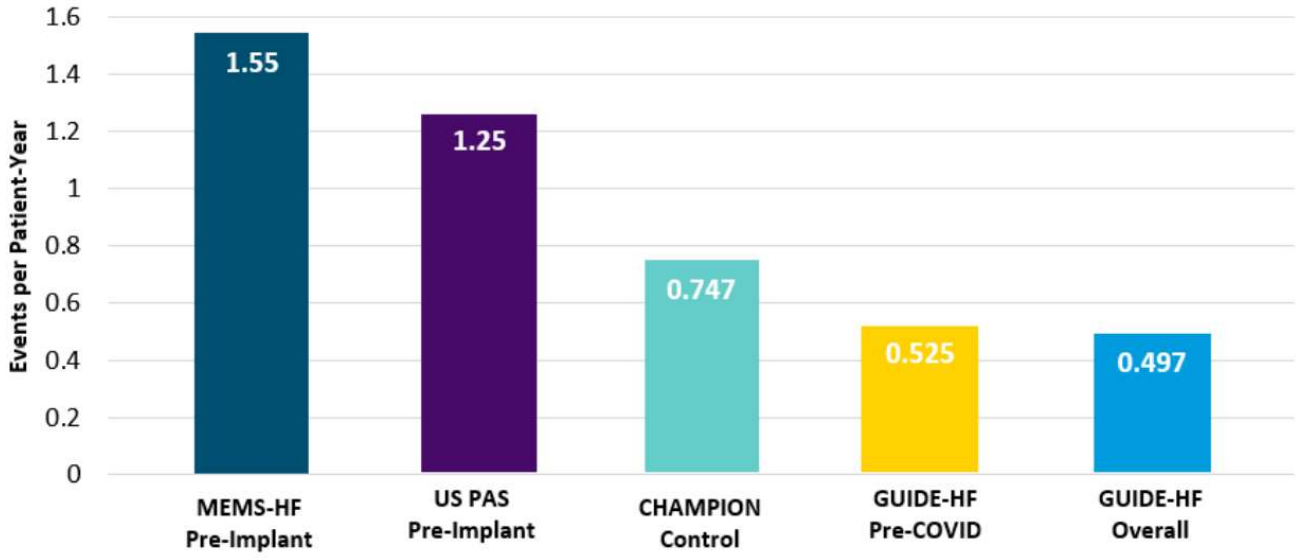
Endpoint	Treatment (N 497) Events (Rate)	Control (N 503) Events (Rate)	Hazard Ratio (95% CI) p value
HF Hospitalization + ED/OP + Death (Primary Endpoint)	**253 (0.563)**	**289 (0.640)**	**0.88 (0.74, 1.05) p=0.16**
HF Hospitalization	185 (0.410)	225 (0.497)	0.83 (0.68, 1.01) p=0.064
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	28 (0.065)	27 (0.063)	1.04 (0.61, 1.77) p=0.89
All-cause Mortality	40 (0.094)	37 (0.086)	1.09 (0.70, 1.70) p=0.71

Figure 22. Cumulative hazard rate curves and 95% CIs for the primary composite endpoint and heart failure hospitalizations



The control group event rate observed overall was lower than trial design event rate assumptions (0.767 vs 0.64), while the treatment group was very close to the assumed rate in the trial design (0.568 vs 0.563).

Figure 23. HF Hospitalization Events Per Patient Year Across PA Pressure Monitoring Studies[54,55,11,12]



Prespecified COVID-19 Analysis

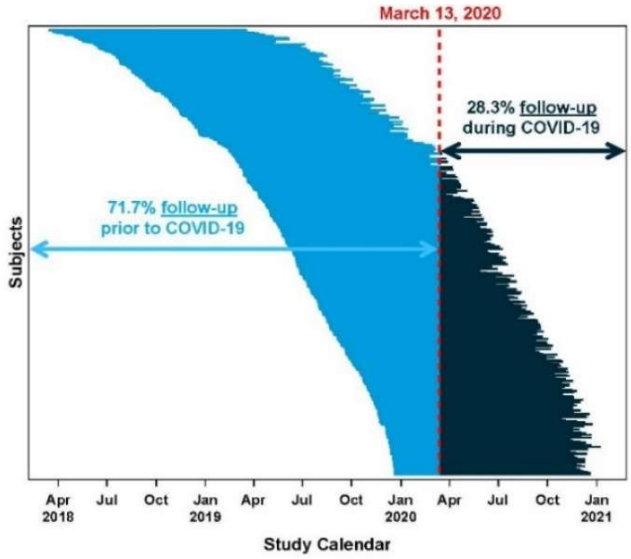
The potential effect of COVID-19 on all aspects of clinical trials has been discussed by the Heart Failure Association of the European Society of Cardiology (ESC-HFA), the European Medicines Agency (EMA), the Heart Failure Collaboratory (HFC), and the FDA. The COVID-19 impact analysis was planned and pre-specified in the amended, FDA-approved statistical analysis plan in August 2020 (5 months before final follow-up). The sensitivity analysis was done to compare events prior to COVID-19 to events during the pandemic. The significance level for interaction was set at 0.15 and approved by the US Food & Drug Administration based on the literature. The interaction p-value was p=0.11, and therefore statistically significant, meaning that the pandemic ***did*** affect the primary endpoint. The pandemic introduced variability into the trial influencing results and data collection in ways that are largely unknown. In discussions with the FDA, there was agreement that it would be appropriate to focus on the pre-COVID-19 period to evaluate the study endpoints.

Table 13. GUIDE-HF COVID-19 Impact Analysis

Analysis Time Period[1]	Treatment (N 497) Events (Rate[2])	Control (N 503) Events (Rate[2])	Hazard Ratio (95% CI), p value[3]	Interaction p value[4]
Prior to COVID-19, Events (Rate)[2]	177 (0.553) n=497	224 (0.682) n=503	0.81 (0.66, 1.00), p=0.049	p=0.11
During COVID-19, Events (Rate)[2]	76 (0.597) n=310	65 (0.536) n=307	1.11 (0.80, 1.55), p=0.53	

72% of the total follow-up days occurred prior to COVID-19 and 28% of follow-up days occurred during COVID-19. All subjects were enrolled and had at least 3 months of follow-up prior to COVID-19, and the median follow-up prior to COVID-19 was 8.4 months.

Figure 24. Follow-up Completed Prior to and During COVID-19



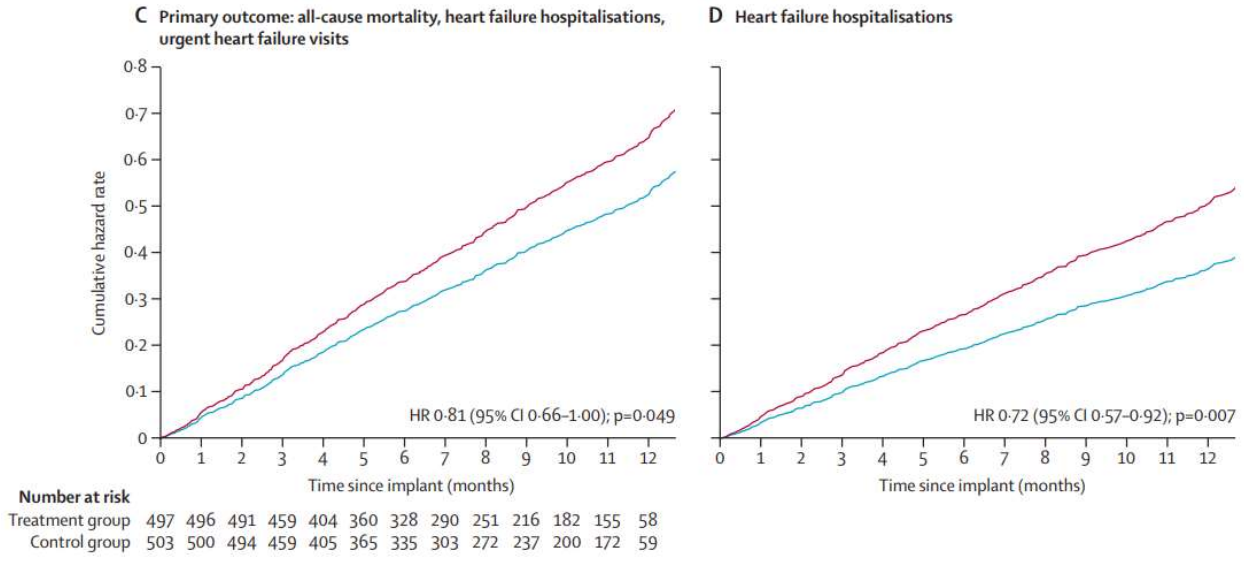
Primary endpoint outcome – Pre-COVID 19 Sensitivity Analysis

In the pre-COVID-19 sensitivity analysis, there was a reduction in primary endpoint events with 177 events (0.553 per patient-year) in the treatment group and 224 events (0.682 per patient-year) in the control group (HR 0.81, 95% CI 0.66–1.00; p=0.049). Similarly, heart failure hospitalizations were reduced with 124 hospitalizations in the treatment group and 176 in the control group (HR 0.72, 95% CI 0.57–0.92; p=0.0072). As in the overall analysis, the study found no differences between groups for either urgent heart failure hospital visits or all-cause mortality before COVID-19.

Table 14. Primary Endpoint and Component Breakdown for pre-COVID 19 Impact Analysis

Endpoint	Treatment (N 497) Events (Rate)	Control (N 503) Events (Rate)	Hazard Ratio (95% CI) p value
HF Hospitalization + ED/OP + Death (Primary Endpoint)	**177 (0.553)**	**224 (0.682)**	**0.81 (0.66, 1.00) p=0.0489**
HF Hospitalization	124 (0.380)	176 (0.525)	0.72 (0.57, 0.92) p=0.0072
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	23 (0.074)	23 (0.073)	1.02 (0.57, 1.82) p=0.95
All-cause Mortality	30 (0.110)	25 (0.088)	1.24 (0.73, 2.11) p=0.42

Figure 25: Cumulative hazard rate curves and 95% CIs for the primary composite endpoint and heart failure hospitalizations, Pre-COVID-19 Analysis

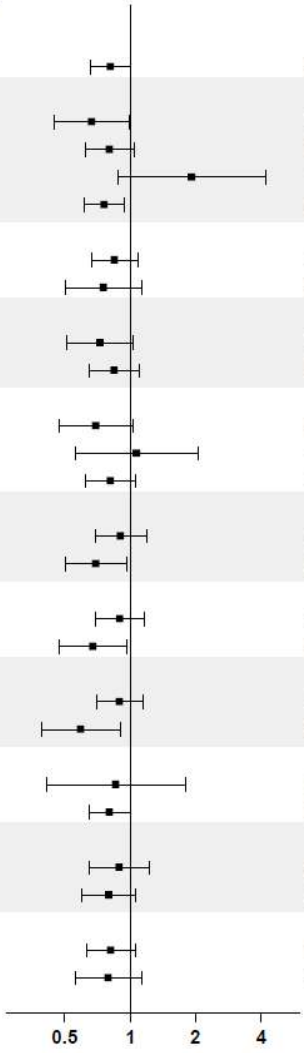


Primary endpoint outcome – Pre-COVID 19 Impact Analysis – Subgroups

Subgroup interactions for the primary outcome were suggested for NYHA functional class (greater treatment effect in NYHA functional Class II or III compared with Class IV), race (greater treatment effect in African American patients), and sex (greater treatment effect in women). Despite noticeably lower event rates in certain subgroups, including patients qualifying via elevated BNP or NT-proBNP, heart failure with preserved ejection fraction, women, and NYHA functional Class II, the study observed a consistent HR for the primary endpoint.

Figure 26. Primary Endpoint Within Subgroups – Pre-COVID-19 Impact Analysis

Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Subgroup p-value	Interaction p-value
Overall	1000	177 (0.553)	224 (0.682)	0.81 (0.66, 1.00)	0.049	
NYHA Class						
NYHA Class II*	296	43 (0.401)	70 (0.603)	0.66 (0.45, 0.99)	0.044	0.074
NYHA Class III	650	114 (0.573)	141 (0.712)	0.80 (0.62, 1.04)	0.10	
NYHA Class IV*	54	20 (2.632)	13 (1.372)	1.92 (0.88, 4.18)	0.10	
NYHA Class II and III*	946	157 (0.507)	211 (0.667)	0.76 (0.61, 0.95)	0.014	0.035†
Qualification						
HFH in year prior*	557	133 (0.747)	166 (0.880)	0.85 (0.66, 1.08)	0.19	0.58
Elevated BNP/NT pro-BNP only*	442	44 (0.329)	58 (0.436)	0.75 (0.51, 1.13)	0.17	
Ejection Fraction						
HFpEF (EF>40%)	469	57 (0.386)	85 (0.531)	0.73 (0.51, 1.03)	0.074	0.50
HFrEF (EF≤40%)	531	120 (0.705)	139 (0.835)	0.84 (0.65, 1.10)	0.21	
Ejection Fraction - Additional						
HFpEF (EF≥50%) *	398	45 (0.349)	71 (0.501)	0.70 (0.47, 1.03)	0.067	0.51
HFmrEF (40%≤EF<50%) *	110	21 (0.691)	19 (0.646)	1.07 (0.56, 2.04)	0.84	
HFrEF (EF<40%)*	492	111 (0.703)	134 (0.866)	0.81 (0.62, 1.06)	0.13	
Age						
Below Median (<71 Years)	492	112 (0.711)	130 (0.786)	0.90 (0.69, 1.18)	0.46	0.22
Median and Above (≥71 Years)	508	65 (0.411)	94 (0.590)	0.70 (0.50, 0.97)	0.030	
Sex						
Men	625	121 (0.636)	139 (0.710)	0.90 (0.69, 1.16)	0.41	0.21
Women	375	56 (0.443)	85 (0.657)	0.67 (0.47, 0.96)	0.029	
Race						
White	807	135 (0.515)	154 (0.576)	0.89 (0.70, 1.14)	0.37	0.091
Black	179	38 (0.740)	70 (1.249)	0.59 (0.39, 0.90)	0.014	
Ethnicity						
Hispanic	33	17 (1.430)	19 (1.665)	0.86 (0.41, 1.80)	0.69	0.84
Non-Hispanic	960	157 (0.522)	202 (0.650)	0.80 (0.64, 1.00)	0.051	
Ischemic Cardiomyopathy						
Ischemic	397	83 (0.629)	87 (0.705)	0.89 (0.65, 1.23)	0.48	0.61
Non-Ischemic	560	91 (0.519)	125 (0.650)	0.80 (0.60, 1.06)	0.12	
Device Implant						
With CRT-D/CRT-P/ICD	562	117 (0.646)	144 (0.792)	0.82 (0.63, 1.06)	0.12	0.92
Without CRT-D/CRT-P/ICD	438	60 (0.436)	80 (0.550)	0.79 (0.56, 1.13)	0.19	



*Non-prespecified Subgroup

†Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Subgroup: NYHA Class IV

NYHA Class IV patients are a complex, highly symptomatic group suffering from advanced heart failure.

- Only 54 patients (5%) patients enrolled in GUIDE-HF were Class IV. This is a small sample size to see treatment benefit.
- Most Class IV patients were enrolled at the end of the trial, resulting in a greater impact due to COVID, and greatly reducing their follow-up time (4.5 months).

No conclusion can be made for Class IV patients from GUIDE-HF. Perhaps, reduction of HF hospitalizations is not the appropriate endpoint to study in this group because of their need for closer management during disease

progression. Further studies are needed to examine this and other endpoints that may give better clinical insight for Class IV patients.

Secondary endpoint outcome – Pre-COVID 19 Impact Analysis

Heart failure events: heart failure hospitalizations plus urgent heart failure hospital visits
In the pre-COVID-19 impact analysis there were 147 total heart failure events in the treatment group and 199 in the control group (0.76, 0.61–0.95; p=0.014).

Health status/Functional Status: KCCQ-12, EQ-5D-5L, 6MWT
The secondary endpoints of GUIDE-HF included quality of life using well-known measures including the KCCQ-12, a cardiovascular specific measure, the EQ-5D-5L, a broad quality of life measure, and the 6-minute walk test, a functional status measure. The paired analyses for the secondary endpoints of KCCQ-12, EQ-5D-5L, and 6MHW at 6 months and 12 months are presented below in Table 15. In both the overall analysis and the pre-COVID-19 impact analysis, the KCCQ-12 and EQ-5D-5L scores improved in both the treatment and control groups at 6 months, with no significant difference between groups. There were no significant changes in functional assessment based on the 6-minute hall walk test observed within or between groups.

For the KCCQ-12 overall summary score, when compared to baseline the study saw significant improvements in both treatment and control groups, but the difference between groups was not statistically significant. However, the treatment group ***exceeded*** the minimally important difference value in the overall summary score of a 5-point change from baseline.

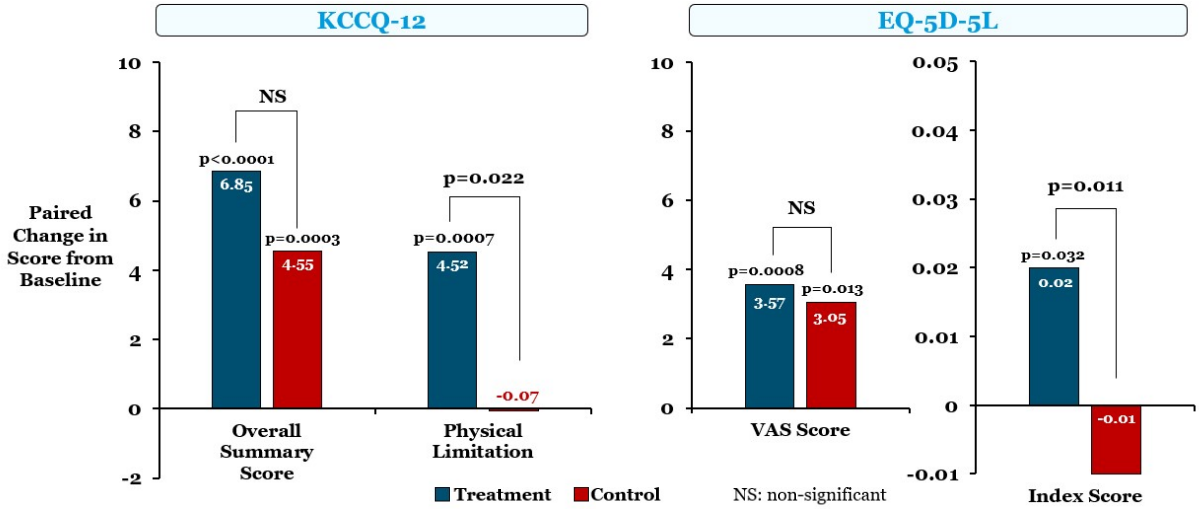
Table 15. Primary Endpoint Within Subgroups – Pre-COVID-19 Impact Analysis

Component/ Analysis	6 Month Paired Change from Baseline			12 Month Paired Change from Baseline		
	Treatment Mean ± SD (n) Within Group p value	**Control** Mean ± SD (n) Within Group p value	Between Group p value	**Treatment** Mean ± SD (n) Within Group p value	**Control** Mean ± SD (n) Within Group p value	Between Group p value
KCCQ-12 Overall Summary Score	6.70 ± 19.69 (319) p<0.0001[2]	4.85 ± 21.58 (318) p<0.0001[2]	0.2588[1]	4.19 ± 18.29 (140) p=0.0076[2]	5.05 ± 22.10 (137) p=0.0084[2]	0.72[1]
EQ-5D-5L Visual Analogue Scale	3.59 ± 18.81 (318) p=0.0007[2]	3.23 ± 21.50 (318) p=0.0077[2]	0.8230[1]	-1.28 ± 20.18 (140) p=0.45[2]	3.89 ± 17.73 (138) p=0.011[2]	0.024[1]
6MHW Test Distance	-2.23 ± 85.04 (281) p=0.66[2]	6.62 ± 94.47 (291) p=0.23[2]	0.2394[1]	-19.46 ± 87.63 (120) p=0.017[2]	-9.78 ± 112.70 (127) p=0.33[2]	0.45[1]

[1]Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[2]Within group change from baseline using one-sample t-test

There were sub-components of both the KCCQ-12 and EQ-5D-5L assessments that showed statistically significant differences when comparing the control and treatment groups of NYHA Class II and III patients. In a sub-component of the KCCQ-12 overall summary score that represents the impact of physical limitations, the study saw a significant improvement in quality of life only in the treatment group, with a significant difference between treatment and control groups. Similarly, the index score of the EQ-5D-5L assessment demonstrated a significant improvement within only the treatment group, and significant difference between groups.

Figure 27. Pre-COVID-19-PHE follow up: NYHA CLASS II AND III Quality of Life Improved at 6 Months



Medication Changes

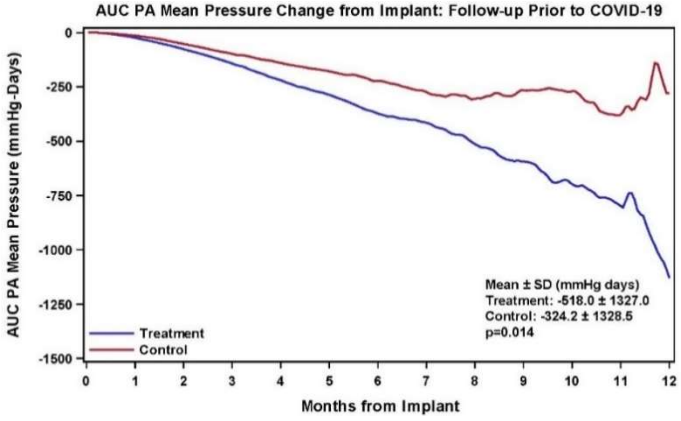
Data regarding medication changes along with the reason for each change were collected in GUIDE-HF. More medication changes were made in the treatment group (1.031 changes per month per patient) compared with the control group (0.608 changes per month per patient) across overall follow-up. Of note, this overall rate for the treatment group includes all medication changes regardless of reason.

When we split into PA pressure-based changes and those based on symptoms, side effects, or other reasons, the study observed that nearly 40% of medication changes in the treatment group were made based on knowledge of PA pressure data, confirming that the treatment group was, in fact, managed using PA pressure and their medications were titrated accordingly. Interestingly, the medication changes due to other reasons occurred at a similar rate between the treatment and control groups, perhaps suggesting standard of care consistent across both groups. We found frequent changes in medications throughout the GUIDE-HF study in both the treatment group and control group. However, more medication changes were made in the treatment group (1·031 changes per month per patient) compared with the control group (0·608 changes per month per patient) across overall follow-up.

Area Under the Curve (AUC)

The pre-COVID-19 analysis also showed a lower mean PA pressure AUC in the treatment group (–518.0 mm Hg-days, SD 1327.0) compared with the control group (–324.2 mm Hg-days, 1328.5; p=0.014 between groups), but with a gradually widening difference over time favoring the treatment group. Of note is that there was an initial lowering of PA pressures in the control group when compared to their baseline. This observation was not seen in CHAMPION.[11,51]

Figure 28. Average PA Mean Pressure Change from Baseline – Area Under the Curve (AUC) – Pre-COVID-19 Impact Analysis



Mortality

While mortality was a component of the primary endpoint, mortality data and determining a mortality benefit was impacted by several factors. Mortality was part of the composite endpoint, but the study was not powered to explicitly establish a mortality benefit on its own.

While it was thought there might be a mortality benefit shown at the original 12-month follow-up time, an additional 28% of that was lost to the COVID-19 pandemic. The 8.4 months median follow-up time in the pre-COVID 19 impact analysis was not long enough to be able to demonstrate the mortality benefit of preventing a decompensation event. In addition, GUIDE-HF included 30% NYHA Class II patients. These patients with less-severe heart failure would not typically contribute significantly to a mortality endpoint within 12 months, regardless of randomized trial group. The trial follow-up was at 12 months. It was not deemed appropriate to implant a device (e.g., control arm) and not use it for longer than 12 months. Additionally, it was felt that patients would not consent to randomization longer than 12 months.

GUIDE-HF Summary

Hemodynamic-guided management across the spectrum of ejection fraction and symptom severity was safe and, in a pre-COVID-19 sensitivity analysis, a benefit of hemodynamic-guided management on the primary outcome, driven by a decrease in heart failure hospitalizations, was demonstrated.

The primary endpoint results were consistent across nearly all subgroups, including those defined by left ventricular ejection fraction, sex, previous heart failure hospitalization, and race, with the possible exception of patients with NYHA class IV heart failure. However, a treatment effect was observed in patients with mild to moderate (NYHA functional Class II–III) heart failure. When aggregated, these data support the observations from other trials. Of important note were the treatment effects for women and African Americans, who are disproportionally affected by HF symptoms and patients with HFpEF who have historically had few treatment options. The potential subgroup interaction for sex differed in direction from that observed in the CHAMPION trial and showed a significant treatment effect in women. Patients with NYHA functional Class IV heart failure did not appear to benefit from hemodynamic-guided management although this subgroup included only 54 patients and the trial might have lacked the ability to show a difference in this small patient cohort. However, the results in these patients were similar to those reported in a previous trial that evaluated hemodynamic management of heart failure.

The observed treatment effect in this study was largely accounted for by a reduction in heart failure hospitalization similar to that observed in previous trials. The observed reduction in heart failure hospitalizations was identical to the 28% decrease reported for patients with NYHA functional Class III heart failure in the CHAMPION trial and consistent with reports of other observational studies, including the CardioMEMS US Post-Approval Study, and clinical trials reporting the benefits of hemodynamic-guided monitoring.[11,54,55] Reductions in PA pressure and heart failure hospitalizations, both of which have been previously associated with a reduction in mortality was observed.

These data affirm and expand the evidence base supporting the benefits of hemodynamic-guided management in patients with chronic heart failure and suggest that such an intervention might be applicable to a broader range of patients, including those with mild to moderate heart failure and those with elevated natriuretic peptides and no previous heart failure hospitalizations.