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STUDY DESIGN

Rationale and design of the CardioMEMS Post-Market Multinational Clinical Study: COAST

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Abstract

Aims Chronic heart failure reduces quality and quantity of life and is expensive for healthcare systems. Medical treatment relies on guideline-directed therapy, but clinical follow-up and remote management is highly variable and poorly effective. New remote management strategies are needed to maintain clinical stability and avoid hospitalizations for acute decompensation.

Methods and results The CardioMEMS Post-Market Study is a prospective, international, single-arm, multicentre, open-label study (NCT02954341) designed to examine the feasibility of haemodynamic guided heart failure management using a small pressure sensor permanently implanted in the pulmonary artery (PA). Daily uploaded PA pressures will be reviewed weekly to remotely guide medical management of patients with persistent NYHA Class III symptoms at baseline and a hospitalization in the prior 12 months. The study will enrol up to 800 patients from 85 sites across the United Kingdom, Europe, and Australia. The primary safety endpoint will assess device or system-related complications or sensor failures after 2 years of follow-up. Efficacy will be estimated after 1 year of follow-up comparing HF hospitalization rates before and after sensor implantation. Observational endpoints will include mortality, patient, and investigator monitoring compliance, PA pressure changes, quality of life, and several pre-defined subgroup analyses.

Conclusions The CardioMEMS Post-Market Study will investigate the generalizability of remote haemodynamic guided HF management in a number of national settings. The results may support the more widespread implementation of this novel clinical management approach.

Keywords Clinical trial; CardioMEMS^{TM} HF System; Haemodynamic monitoring; Heart Failure; Pulmonary artery pressure

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Introduction

The number of patients with chronic heart failure (HF) is increasing at an alarming rate with estimates that one in five people will develop HF in their lifetime.[1–3] Prevalence is expected to nearly double by the year 2030. Chronic HF is a clinical syndrome characterized by the heart's inability to provide adequate flow to meet the body's needs, particularly on exertion.[1,2] This syndrome arises from myocardial dysfunction resulting in a mixture of decreased contractility during systole (HF with reduced ejection fraction, HFrEF) or an inability to appropriately fill the ventricles during diastole (HF with preserved ejection fraction, HFpEF) with resultant neurohormonal activation. Elevated pulmonary artery (PA) pressures are common features of both HFrEF and HFpEF[4] and are associated with the subsequent increased risk for mortality[5] or decompensation requiring hospitalization.[6] Lowering PA pressures is directly associated with improved outcomes.[5,6]

Over 90% of hospitalized patients complain of severe and worsening congestion symptoms, such as lifestyle limiting exertion intolerance due to dyspnea or fatigue.[7] These symptoms correlate to elevated PA pressures from increased intravascular volume and/or pulmonary vascular resistance. Therapies used to reduce intravascular volume, such as

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diuretics, alleviate symptoms and help to maintain clinical stability, allowing patients to resume normal activities outside the hospital. However, a high percentage of patients experience rapidly recurring symptoms requiring rehospitalization shortly after discharge.[7] Several clinical management strategies designed to closely monitor for evidence of accumulating volume or early detection of symptoms have been tested with the goal of reducing the need for hospitalization, by acting on changes in a remotely monitored signal, such as daily weight measurements, patient reported symptoms,[8–12] B-type natriuretic peptide levels,[13] or non-haemodynamic physiologic signals derived from implanted devices, such as intrathoracic impedance.[14–18] Unfortunately, most studies failed to reduce the need for HF hospitalizations, but a minority have suggested the potential for an improvement in survival in closely monitored patients.[8,12]

There remains a clinical need for innovative remote monitoring tools (acceptable to patients and physicians) that can guide clinical management and effectively reduce HF hospitalization rates.[19] The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association (NYHA) Class III HF patients trial (CHAMPION, ClinicalTrials.gov NCT00531661) was a prospective, randomized single-blinded clinical trial that utilized remotely obtained PA pressures, measured daily and reviewed weekly, to guide medical management of previously hospitalized symptomatic patients with HF, regardless of ejection fraction.[20] Pulmonary artery pressure guided care was superior to traditional clinical management strategies resulting in more pressure guided medication changes, significant reduction in PA pressure, clinically meaningful reductions in HF hospitalizations, and improved quality of life.[21] All primary and secondary endpoints in the CHAMPION trial were significantly improved in favour of the haemodynamic monitored group, including a 50% reduction in hospitalization rates in patients with HFpEF,[22] representing the first intervention that clearly improved clinical outcomes in this group patients who can be difficult to manage. A strong trend toward improved survival was seen in the HFrEF group studied in CHAMPION.[23] Subsequent real-world data in thousands of patients demonstrate similar outcomes to those reported in the CHAMPION pivotal trial.[24–26] Most recently, large propensity matched analyses in real-world cohorts found that haemodynamically monitored patients with HF had significant reductions in days lost due to death or hospitalization, with associative improved survival in the monitored group.[26]

Haemodynamic guided HF management with remote PA pressure monitoring, however, was predominantly tested in the United States healthcare system. The PA pressure monitoring system (CardioMEMS™ HF System, Abbott, Atlanta, GA, USA) has the CE mark and Therapeutic Goods Administration approval and is modelled to possibly be cost-effective in other geographies.[27] Additionally, the CardioMEMS™ HF System has Food and Drug Administration approval based on the safety and efficacy demonstrated in the CHAMPION Trial. Demonstration of the feasibility of utilizing remote PA pressure monitoring in other healthcare systems is required to support worldwide implementation of this management strategy. Health-care systems including patients, providers, and governmental regulatory or reimbursement agencies vary significantly across geographies. Practical considerations, such as regional cellular connectivity, patient's willingness to be frequently monitored, availability of health-care providers with expertise and structured workflow to monitor remotely obtained data may influence the effect of hemodynamic guided HF care. The current report describes the design of a unified multinational clinical investigation implemented to examine if PA pressure monitoring is feasible in the diverse healthcare systems in the United Kingdom, Australia, France, and other European countries. Similar, but separate investigations are ongoing in Germany, the Netherlands, and Ireland.[28,29]

Study design

The CardioMEMS Post-Market Study (COAST) is a prospective, multicentre, international, and open-label clinical investigation conducted in up to 85 sites in centres located in the UK, Europe, and Australia. The purpose of this real-world study is to evaluate the feasibility of utilizing remote PA pressure monitoring (CardioMEMS™ HF System) to guide outpatient medical management of patients with predominantly NYHA Class III HF symptoms and a previous hospitalization. This implantable sensor system is well described elsewhere and previously validated.[20,21]

The study will be conducted over approximately 60 months (approximately 18 months enrolment plus 24 months follow-up for each country included in the study). The PA sensor will be implanted in all patients who will then receive education specific to uploading resting, supine pressure information using an interrogation pad specifically designed for home use. Investigators will review uploaded PA pressure measurements on a secured website database (Merlin.net™ patient care network, Abbott, Sylmar, CA, USA) at least weekly. Investigators will utilize the pressure information to guide medication adjustments to lower PA pressures, if abnormally high, and respond to pressure increases that may occur over time. Follow-up study visits will be scheduled at Month 1, Month 6, and every 6 months thereafter for 2 years following PA pressure sensor implant. In addition to official study visits, frequency, purpose, and outcome of all contacts between site staff and study subjects post implant will be recorded. The study protocol is consistent with the Declaration of Helsinki and approved by ethics committees at each institution involved.

Inclusion/exclusion criteria

Study subjects will have a history of at least one HF hospitalization over the previous 12 months with persistent NYHA class III symptoms over the previous 30 days regardless of ejection fraction. Subjects must be able to tolerate dual antiplatelet therapy with aspirin and clopidogrel for 30 days following implant of the PA sensor. Only low-dose aspirin will be required for patients with an indication for warfarin or a direct oral anticoagulant agent. All eligible subjects 18 years of age or older will provide written informed consent. Subjects with HFrEF must be treated with maximally tolerated guideline-directed medical therapy (GDMT)[2] for 1 month prior to PA pressure sensor implantation and for 3 months after cardiac resynchronization therapy. Intolerance to GDMT must be documented prior to enrolment. Subjects with reduced glomerular filtration rate (GFR $<$ 25 mL/min) who are non-responsive to diuretic therapy or who are on chronic renal dialysis are excluded from the study. *Table 1* provides a complete listing of exclusion and inclusion criteria for the study.

Primary and secondary endpoints

The primary safety endpoint includes freedom from device- or system-related complications and freedom from pressure sensor failure after 2 years of follow-up. The primary safety hypotheses are that the device/system-related complication-free proportion of subjects will be at least 80% at 24 months and that the pressure sensor failure-free proportion of subjects will be at least 90% at 24 months. A device- and/or system-related complication is defined as an adverse event that is, or is possibly, related to the system (wireless pressure sensor or external electronics) and has at least one of the following characteristics: is treated with invasive means (other than intramuscular medication or a right heart catheterization that is used for diagnostic purposes); results in the death of the subject; or results in the explant of the device. Safety will also be assessed throughout the study by recording and reviewing the frequency of Adverse Device Effects, Serious Adverse Events, and Serious Adverse Device Effects (Table *2*).

The primary efficacy endpoint will compare the annualized HF hospitalization rate at 1 year in the study to the HF hospitalization rate in the year prior to enrolment. Supplemental analyses include mortality at 1 year, HF hospitalization or death at 1 year, patient compliance over the trial, training evaluation, health-related quality of life measured using the EuroQOL Five Dimensions Questionnaire, and various subgroup analyses. Change in pressure over time will be analysed using an area under the curve methodology previously described.[20,21] The total number of PA pressure readings taken will be reported as a percentage of patient days at home. Efficacy analyses will be performed in various subgroups, including women, men, reduced ejection fraction ($<$40%), preserved ejection fraction ($\geq$40%), ischemic aetiology, non-ischemic aetiology, subjects with or without implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator, and GFR.

Table 1 Inclusion and exclusion criteria

Inclusion criteria (if all of the following met)	Exclusion criteria (if any one of the following met)
1. Written informed consent obtained from subject	1. Subjects with an active infection
2. $\geq$18 years of age	2. Subjects with history of recurrent ($>$1) pulmonary embolism or deep vein thrombosis
3. Diagnosis of NYHA Class III Heart Failure	3. Subjects who, in the investigator's opinion, are unable to tolerate a right heart catheterization
4. At least 1 HF hospitalization within 12 months of baseline visit	4. Subjects who have had a major cardiovascular event (e.g. myocardial infarction, open heart surgery, stroke, etc.) within 2 months of baseline visit
5. Subjects with reduced LVEF heart failure should be receiving a beta blocker for 3 months and an ACE-I or ARB for 1 month unless in the investigator's opinion, the subject is intolerant to beta blockers, ACE-I, or ARB.	5. Subjects with a cardiac resynchronization device (CRT) implanted $<$3 months prior to enrollment
6. Subjects with a BMI $\leq$ 35. Subjects with BMI $>$ 35 will require their chest circumference to be measured at the axillary level; if $>$65 inches, the patient will not be eligible for the study.	6. Subjects with a glomerular filtration rate (GFR) $<$ 25 ml/min (obtained within 2 weeks of the baseline visit) who are non-responsive to diuretic therapy or who are on chronic renal dialysis
7. Subjects with pulmonary artery branch diameter$\geq$ 7 mm—(implant target artery—assessed during the RHC)	7. Subjects with congenital heart disease or mechanical right heart valve(s)
8. Subjects willing and able to comply with the follow-up requirements of the study	8. Subjects likely to undergo heart transplantation or VAD within 6 months of baseline visit
	9. Subjects with known coagulation disorders
	10. Subjects with a hypersensitivity or allergy to aspirin and/or clopidogrel (not applicable for subjects taking anticoagulation therapy or other approved antiplatelet therapy).

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; HF, heat failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RHC, right heart catheterization; VAD, ventricular assist device.

Table 2 Schedule of events

	Screening	Baseline (implant)	Month 1	Month 6 and every 6 months thereafter until study termination
Procedures	Prior to implant	(Within 30 days of screening)	Visit 1 (30 ± 7 days)	Visits 2–5 or study termination (±30 day window)
Informed consent	X			
Demographics	X			
Past medical and surgical history. Ejection fraction is part of this assessment and must be obtained within 6 months of the baseline visit or prior to implantation.	X			
Inclusion/exclusion criteria review	X	X		
GFR (within 2 weeks of the implant procedure)	X			
INR (if indicated)		X		
Pulmonary artery measurement		X		
Physical examination (including weight)	X[a]	X[b]	X[b]	X[b]
NYHA HF classification	X		X	X
Pulmonary artery angiography		X		
Sensor implant		X		
Sensor measurements		X	X (investigator discretion)	X (investigator discretion)
Adverse events assessment		X	X	X
HF hospitalizations	X		X	X
Quality of life assessment (EQ-5D-5L)	X			X (6, 12, 18, 24 months)
Medication assessment (heart failure)	X	X	X	X
Subject contact log[c]			X	X

EQ-5D-5L, EuroQOL Five Dimensions Questionnaire; GFR, glomerular filtration rate; HF, heart failure; INR, international normalized ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]Includes weight, height, and vital signs (temperature, blood pressure, and pulse).
[b]Includes weight, vital signs, and significant changes from previous physical examination.
[c]To be completed each time contact is made between the site staff and a study subject.

Statistical analyses

For the 2 year primary safety endpoint of freedom from device-related complications, using an exact one-sided test for one-sample binomial proportions with alpha of 0.025 (equivalent to two-sided test at alpha of 0.05), a sample size of 137 subjects will provide greater than 90% power to detect a difference as small as 10% from the null proportion rate of 0.80 (i.e. objective performance criterion of 80%). A sensor failure occurs when no readings can be obtained from the sensor after troubleshooting the system to rule out any problems with the external electronics. For sensor failures at 2 years, a sample size of 292 subjects provides greater than 90% power to detect a difference as small as 5.0% from the null proportion rate of 0.90 (i.e. objective performance criterion of 90%).

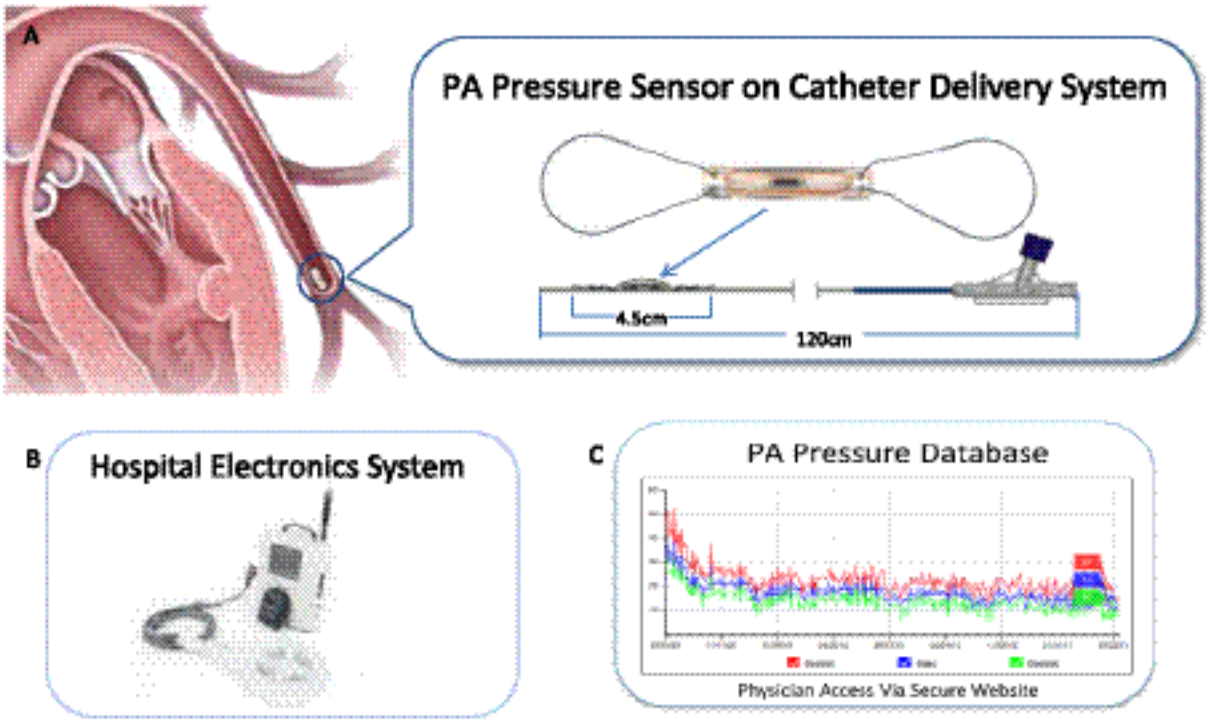
For the primary efficacy endpoint of HF hospitalization rate after 1 year, 250 subjects will provide greater than 90% power to meet the efficacy goal, using a one-sample, one-sided Poisson rate test with alpha of 0.025. For this study, HF hospitalization rates at 1 year will be compared with the rate observed in the trial subjects 1 year prior to enrolment (i.e. 1.0 or greater). Using a one-sample, one-sided Poisson rate test with alpha of 0.025 (equivalent to two-sided test at alpha of 0.05), at least 149 subjects will provide >90% power to show a difference between a *treatment* rate as high as 0.75 (conservative estimate) and the subject's own historical rate from the year prior estimated at a minimum of 1.0.

To allow up to approximately 100 patients per country to be enrolled at up to seven countries and to account for a 10–15% early withdrawal rate, the planned enrolment for the study is up to 800 patients. The exact number of countries and number of patients per country is not pre-specified in the protocol.

Study device

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring PA pressure and heart rate in New York Heart Association (NYHA) Class III HF patients who have been hospitalized in the previous 12 months. The system provides the physician with the patient's PA pressure waveform including systolic, diastolic, and mean pressures as well as heart rate. Haemodynamic data are used by physicians for HF management with the goal of reducing HF hospitalizations. The system is comprised of an implantable wireless microelectromechanical sensor, which is empowered by interrogation and does not require an indwelling lead or battery. The sensor is permanently implanted into the distal

Figure 1 The CardioMEMS TM HF System sensor is permanently implanted into the distal pulmonary artery (PA) using transcatheter techniques in the catheterization laboratory (A); the sensor baseline is set to the mean PA pressure using a pulmonary artery catheter. Daily PA haemodynamic measurements are taken by the patient in a supine position at home. The patient measurement system consists of an antenna and electronics unit that guides the patient through the short reading process (B). The data can be recorded from the home, hospital, physician's office, or clinic. The haemodynamic data is transmitted to the website which is accessible via a secure website to the patient's heart failure clinician (C).



PA using transcatheter techniques and fluoroscopic guidance. A patient electronics system will be used to collect daily PA haemodynamic measurements; an electronics system for hospital use is available, and a patient database (Merlin.net website) will be accessible via a secure access by the patient's HF clinician (*Figure 1*).

During interrogation of the implanted sensor using a hospital or patient electronics unit, radiofrequency energy is emitted from an external antenna used to empower the implanted sensor. At the implant procedure, the sensor is calibrated to the mean PA pressure using simultaneous measurements from the sensor and a PA catheter.

Training

In general, remote haemodynamic monitoring requires patient adherence to daily uploads and timely provider review of trended pressures leading to a decision about medication changes. Provider–patient communication is essential to ensure that patients understand and implement any changes in lifestyle or medications that may arise from monitoring. Finally, patients must understand that medication changes may be based on haemodynamic information and not necessarily on symptoms. Each facet of this workflow is required for successful remote management, and the concepts are included in provider and patient education.

Following the sensor implant procedure, subjects and their caregivers, if possible, will be instructed on how to take their own PA pressure measurements using the patient electronic unit. All investigators and clinical investigation personnel will attend training sessions detailing the implant, use, and follow-up of the haemodynamic monitoring system. Investigators are instructed to carefully review haemodynamic information from the baseline right heart catheterization at the time of implant to have a clear understanding of intravascular volume, vascular resistance, and diastolic transpulmonary gradient. These data guide both short- and long-term medical decision-making. Pulmonary artery pressure goals, initially set to normal values in the Merlin.net system, are individualized along with the notification thresholds. Thresholds account for normal pressure variability and define the range of pressures the physician considers acceptable. Typically, defining individual pressure goals and thresholds is a process that takes several weeks of medication adjustment with remote haemodynamic feedback to reach appropriate status. General guidance recommends more frequent pressure reviews in the first 3–6 months following

implantation of the sensor to reach pressure goals. The treatment goal of the 'optimization phase' is to restore PA pressures to normal if possible. Short term reductions in pressures can be achieved by addressing excess intravascular volume by intensifying diuretics while careful titration of vasodilators to lower vascular resistance is a longer-term goal. These efforts typically require 3–6 months of frequent medication changes and pressure reviews after which the number of medication changes typically decrease by 50%. After establishing a goal and appropriate range of pressures around that goal (accounting for typical day-to-day natural variability), investigators are encouraged to transition into a 'maintenance' strategy dominated by management by exception by focusing on patients with excursions out of the individualized ranges. Investigators *are* automatically notified if the user defined pressure thresholds are crossed. Medication changes to lower *PA* pressures will include adjustments in diuretics and vasodilators, while threshold crossings are usually treated by adjusting diuretic dosing.

Discussion

The COAST is designed to evaluate feasibility of haemodynamic guided HF management using the CardioMEMS™ HF System in a variety of healthcare systems. The protocol is designed to provide a unified methodology across several countries that will allow poolable analyses but also satisfy unique local regulatory or reimbursement requirements. The goal of haemodynamic guided HF management is to reduce episodes of clinical decompensation requiring hospitalizations based on observations that hospitalizations correlate with disease progression, clinical decline, and mortality.[30] Haemodynamic guided HF management relies on the concept that abnormal PA pressures correlate directly with increased HF hospitalization[6] and mortality risk[5] thus remotely providing insight and direction for long-term management. Additionally, the protocol is based on observations that PA pressures increase from baseline several weeks before patients develop symptoms or change in daily weight measurements leading to hospitalization. It is crucial to demonstrate that this approach is feasible in other healthcare systems in which infrastructural support for remote monitoring of HF patients may vary.

Previous remote monitoring trials relied on a variety of systems designed to identify patients at high risk for decompensation. These systems remotely provided information about changes in daily weight measurements, early detection of congestion symptoms, coupled with frequent patient contact.[8–12] Other protocols relied on remote monitoring of device-based diagnostics, such as intrathoracic impedance or heart rate, to guide clinical management measurement.[14–18] HF disease management strategies have also focused on frequent measurement of BNP or N terminal pro BNP to guide medical therapies.[13] Results from these clinical management studies are variable with inconsistent impact on hospitalization rates even though many of the monitored parameters are retrospectively correlated with HF events. Several speculative explanations potentially explain the failure of previous remote monitoring trials. However, the central theme is that a remotely obtained signal must not only identify high-risk individuals but should also provide information to guide appropriate changes in medical therapies along with data about resolution of the high-risk status.[31] It is equally important that physicians act on the data and review the *effect* of such actions. Not surprisingly, tailoring diuretic doses and vasodilator use are the most common medication groups used to haemodynamically manage ambulatory patients with HF.[32] Thus far, managing patients with HF, regardless of left ventricular ejection fraction, based on remotely obtained PA pressures is the only clinical management strategy that consistently lowers hospitalization rates, improves quality of life, and decreases days lost to death or hospitalization.

Haemodynamic guided HF management has sound physiologic plausibility as an effective means to reduce decompensation events and lower risk for disease progression in ambulatory HF patients. In fact, a recent report from the HFrEF patients in the CHAMPION trial discovered a synergy between haemodynamic guided care and the effectiveness of neurohormonal antagonism, with the best outcomes in those already receiving maximally tolerated GDMT at target doses.[23] Furthermore, outcomes from the pivotal prospective randomized trial are consistent with those found in large database analyses suggesting this management strategy is generalizable to US clinical healthcare delivery systems.[31] Importantly, haemodynamic guided care is the only intervention and treatment strategy to demonstrate improved outcomes in patients with HFpEF.[22] Clearly, this is physiologically plausible as filling pressures in this group are labile and tend to change more rapidly prior to acute decompensation compared to HFrEF patients.[5] These concepts are currently being tested in a broader population of less or more symptomatic HF patients (NYHA Class II or IV) who either have a previous hospitalization or elevated BNP levels in a large prospective randomized clinical trial in the United States and Canada.[33] The central hypothesis tested in the Hemodynamically GUIDEd Heart Failure Management (GUIDE-HF) trial is that primary prevention of the first hospitalization may offer survival benefit in symptomatic HF patients with evidence of congestion.[33]

In addition to gathering safety and efficacy data from a variety of national healthcare systems, the COAST is designed to investigate the feasibility of haemodynamic guided HF management throughout the world. Worldwide HF management is heterogeneous with substantial differences in use of GDMT drugs and frequent suboptimal dosing of medication.[34] Also, the use of implantable devices, such as cardiac

resynchronization therapy with or without a defibrillator, varies significantly from country to country. In addition to therapeutic interventions, outcomes and costs of care differ substantially worldwide. Therefore, the COAST Study is designed to transcend borders and discover if a specific HF management strategy using frequent remote assessment of PA pressures translates to potential benefit in multiple clinical settings.

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