SELFIe-HF

PATIENT SELF-MANAGEMENT WITH HEMODYNAMIC MONITORING: VIRTUAL HEART FAILURE CLINIC AND OUTCOMES

A preliminary study in high risk patients

Protocol Number: MHICC-2018-001

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DATE OF PROTOCOL*:* ***01-JUN-2020***

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Protocol Title: Patient SELF-management with hemodynamIc monitoring: Virtual Heart Failure Clinic and Outcomes. A preliminary study in high risk patients

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I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

By signing below, I hereby declare that I am not debarred, disqualified, or otherwise restricted by any agency from conducting any research studies.

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Site Name: Montreal Heart Institute

Synopsis

Title	Patient' SELF-management with HemodynamIc monitoring: virtual Heart Failure clinic and outcomes (the SELFIe-HF trial): program.
Investigator Device	CardioMEMS™ HF System
Study objectives	To demonstrate that a virtual Heart Failure Clinic (HFC) based on patient self-management using Pulmonary Artery Pressure (PAP) monitoring is superior to usual care of HFC, leads to decreased: hospital admissions for heart failure (HF), emergency department consultation and/or unplanned intravenous heart failure therapy and cardiovascular death, compared to a regular HFC, has low device-related complications and is cost-effective, in New York Heart Association (NYHA) class III and II (requiring diuretics) patients.
Study design	This will be a single center, prospective, randomized, open-label blinded-endpoint (PROBE) trial in which the treatment group will be implanted with a CardioMEMS HF sensor and managed using remote access to hemodynamics compared to a non-implanted control group. Patients with at least one hospitalization for HF (≥1) in the previous year (12 months) will be randomized into two groups, regardless of LVEF: ▪ Usual care with the specialized multidisciplinary HF clinic team (Non-implanted Control) or ▪ Hemodynamic monitoring, less intense HF clinic follow-up, and remote follow-up by a nurse clinician and patient empowerment with access to the PAP data (CardioMEMS group). Primary and secondary endpoints will be compared between groups after 12 months of follow-up and within groups comparing baseline parameters with 12 month follow-up measurements.
Key Inclusion criteria	1. Male or female ≥ 18 years old 2. Symptomatic HF (NYHA III) with recent heart failure admission in the previous year (12 months). or 3. Patient with at least one ER visit or unplanned HF clinic requiring iv diuretics within 12 months will be eligible if they have in addition a N-terminal pro-BNP (NT-proBNP) level > 800pg/ml at screening AND NYHA Class II on diuretics (furosemide ≥ 40mg qd), III or ambulatory IV. 4. HF with reduced or preserved EF of at least 3 months duration. 5. Minimum technological knowledge either with a smartphone or iPAD for use of the self-management application, including access to internet.

	6. Anatomical criteria a. PA branch diameter between 7 mm – 15 mm b. For BMI >35, distance from patient's back to the target PA<10 cm.
Key exclusion criteria	1. Recent cardiovascular events: Acute coronary syndrome, percutaneous coronary intervention (PCI), new cardiac rhythm management (CRM) device (pacemaker, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT)), CRM system revision, lead extraction or cardiac or other major surgery or transient ischemic attack or stroke within 2 months (3 months for CRT or cardiac surgery). 2. Scheduled cardiac surgery; 3. History of pulmonary embolism or recurrent deep vein thrombosis 4. Persistent NYHA Class IV and American College of Cardiology (ACC)/ American Heart Association (AHA) HF Stage D, patients implanted with a ventricular assist device (VAD), or patients listed for cardiac transplantation and likely to be transplanted within 12 months 5. Coexisting severe obstructive valvular lesions, obstructive hypertrophic cardiomyopathy, endocarditis, tamponade or large pericardial effusion 6. Clinically too unstable to be followed remotely; this includes but is not limited to: a) Resting systolic blood pressure < 80 or > 180 mmHg; b) Resting heart rate > 100 bpm; c) Stage IV or V chronic kidney disease (Estimated Glomerular Filtration Rate (eGFR) that remains < 30mL/min/1.73m^2 by MDRD) or nonresponsive to diuretic therapy or on chronic renal dialysis; 7. Severe pulmonary hypertension with systolic pulmonary artery pressure ≥ 80 mmHg. 8. Pulmonary hypertension other than group II PH; 9. Anemia requiring transfusions, iron infusions, or hemoglobin below 100; 10. Coagulopathy or uninterruptible anticoagulation therapy or contraindication to antiplatelet/anticoagulant treatments anticipated in the protocol; 11. Intolerance to aspirin or clopidogrel; 12. Active infection requiring systemic antibiotics; 13. Life expectancy <1 year;

Primary Endpoint	The primary endpoint is the time to first occurrence of any component of the composite event as adjudicated by the Clinical Event Committee (CEC). Components of the event are: acute decompensated heart failure requiring emergency department consultation and/or unplanned intravenous heart failure therapy in an outpatient clinic, or hospital admission for heart failure or cardiovascular (CV) death during 12 months of follow-up.
Secondary Endpoints	• Time to the first occurrence of the individual components of the primary endpoint • Changes from baseline in functional ability: o NYHA class o Health-related Quality of life, as measured by a HF-specific instrument (KCCQ) o 6-minute walk distance • Cost-effectiveness • Device related endpoints o Safety: adverse events related to the device o Number of successful patient contacts (virtual and clinic) o PA pressures: changes, frequency of elevated readings o Ease of application utilization.
Tertiary/ Exploratory endpoints	• Goal for best practice o % achieved target dose of guidelines derived medical therapy (GDMT) (HF with reduced ejection fraction (HFrEF)) o Medication changes (mean dose achieved by class) o Time (days) to achieve target doses of GDMT (HFrEF) • Changes in cardiac remodeling assessed by echocardiography between baseline and 12 months: o indexed LV End-systolic and end-diastolic volumes (LVESVi, LVEDVi), left ventricular ejection fraction (LVEF) o Right ventricle (RV) dimensions and function, o Left atrium volume o mitral and tricuspid regurgitation severity • Changes in specific biomarkers for heart failure • Arrhythmia burden • Patient quality of life and satisfaction regarding both the virtual follow-up itself & the personalized algorithm using the application. • Sample for drug concentrations
Control Group	Eligible patients who agreed to participate and provide informed consent that are randomly assigned to the control group will be followed using standard clinical management at the Montreal Heart Institute specialized HF clinic.

CardioMEMS Group	Eligible patients who provide informed consent and randomized to the intervention group will be implanted with the CardioMEMS HF System and instructed to use the Patient Electronic System. In addition, patients will be provided the MyCardioMEMS smartphone app, which will include PA pressure information and instructions for any changes in therapy.
Number of subjects	150 patients with 1:1 randomization
Plan for statistical analysis	For the primary endpoint, the analysis will be an unadjusted comparison of time to first event. Event-rate curves will be estimated by the Kaplan-Meier product-limit method and the difference between groups will be assessed using the log-rank test. Components of the primary endpoint will be analyzed similarly. ANCOVA models will be used to compare the secondary endpoints expressed as a change from baseline to 12 months between groups. The models will include fixed effects for group and baseline value as a covariate. Difference between groups in other continuous endpoints will be tested by either two-sample t-tests or Wilcoxon rank-sum tests depending on the distribution of the data. Chi-square tests will be used for categorical endpoints. All statistical tests will be two-sided and conducted at the 0.05 significance level. Statistical analysis will be done using SAS version 9.4 or higher.

List of abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ARO	Academic Research Organization
BMI	Body Mass Index
BPM	Beat Per Minute
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
BSA	Blood Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCTN	Canadian Cardiac Transplantation Network
CEC	Clinical Event Committee
CardioMEMS	Heart sensor Allows Monitoring of Pulmonary Pressures
CHAMPION	Heart Failure Patients Trial
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRM	Cardiac Rythm Management
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
ED	Emergency Department
EF	Ejection Fraction
ePAD	estimated Pulmonary Artery Diastolic
ER	Emergency Room
ERA	Endothelin Receptor Antagonist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDMT	Guidelines Derived Medical Therapy
H	Hour
HF	Heart Failure
HFC	Heart Failure Clinic
HfpEF	Heart Failure with preserved Ejection Fraction
HfrEF	Heart Failure with reduced Ejection Fraction
HFDMP	Heart Failure Disease Management Program

HR	Heart Rate
hs-CRP	high-sensitivity C-Reactive Protein
ICD	Implantable Cardioverter Defibrillator
ICER	Incremental Cost- Effectiveness Ratio
IEC	Independent Ethic Committee
IHM	Implanted Hemodynamic Monitor
IRB	Institutional Review Board
LA	Left Atrium
LAP	Left Atrial Pressure
LV	Left ventricle
LVEF	Left Ventricular Ejection Fraction
LVESi	Left Ventricular volume indexed to BSA
MDRD	Modification of Diet in Renal Disease
Mg	Milligram
Min	Minute
mL	Milliliter
mmHg	millimeters of mercury
Mmol	Millimol
MHI	Montreal Heart Institute
MHICC	Montreal Health Innovations Coordinating Center
MLHF	Minnesota Living With Heart Failure
MRA	Mineralocorticoid Receptor Antagonists
NT-proBNP	N-terminal prohormone B-type Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary Artery
PAP	Pulmonary Artery Pressure
PCI	Percutaneous Coronary Intevention
PCWP	Pulmonary Capillary Wedge Pressure
PDE5I	Phosphodiesterase 5 Inhibitors
PH	Pulmonary Hypertension
PIIINP	Procollagen type III N-terminal Propeptide
pg/ml	Picogram per millilter
PROBE	Prospective Randomized Open-label Blinded-Endpoint
PVR	Pulmonary Vascular Resistance
QALY	Quality Adjusted Life Year
Qd	*quaque die* (every day)
QOL	Quality Of Life
RHC	Right Heart Catherization
RV	Right Ventricle
SAE	Serious Adverse Event
SGCS	Solube guynylate cyclase stimulators
SID	Subject identification number
VAD	Ventricular Assist Device
VT/VF	Ventricular Tachycardia/Ventricular Fibrillation
WHO	World Health Organization

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1.0 RATIONALE

1.1 Background

Heart failure (HF) represents a major public health concern and its incidence will continue to rise as the population ages. The growing burden of HF on healthcare costs is well documented.[1] Despite major advances in diagnosis and treatment, HF is associated with high rates of decompensation, hospitalization and mortality. Developing new approaches for patients with HF are essential. In the past, major efforts have been directed toward reducing length of stay by the development of performance measures, with the intent to improve post-discharge outcomes.[2,3] Recently, however, the focus has shifted towards 30-day post-discharge readmission rates as a measure of quality of care due to important changes in reimbursement patterns in the US.

Congestion is one of the hallmarks of HF hospitalizations and an increase in body weight seems to be associated with HF-related hospitalizations, usually beginning at least one week before admission for acutely decompensated heart failure (ADHF).[4] Consequently, increased daily weight may identify a high risk period during which one can intervene to avert ADHF requiring hospitalization.[5]

In addition to congestion, the presence of pulmonary hypertension (PH) secondary to heart failure, classified as World Health Organization (WHO) Group 2 PH[6] is associated with increased morbidity and mortality.[7] Therefore, in theory, an elevated pulmonary artery pressure (PAP) and increased pulmonary vascular resistance (PVR) should represent meaningful triggers for therapeutic interventions, and the reduction of decompensated HF an attractive therapeutic target.

HF management programs which rely on patients' empowerment through education and careful follow-up, as well as pharmacological and device-optimization have been shown to decrease hospital admissions, emergency consultations, improve quality of life and probably survival.[8] Unfortunately, due to resource limitations and the increasing number of patients with moderate to severe heart failure, the majority of patients that could benefit from follow-up in multidisciplinary heart failure clinics (HFC) do not readily have access to them in a timely manner.[9] Innovative approaches might be crucial to changing the emphasis of the HFC and processes. New transitional models for HF care have been developed, such as structured telephone care (or telehealth) with

symptoms and vital signs monitoring, home visits, use of technology and remote monitoring systems to reduce HF-related hospitalizations, but with mixed results.[10-12] Recently, the BEAT-HF trial failed to show a benefit for 30 and 180 days readmission or mortality using a combined approach of health coaching telephone calls and telemonitoring with electronic equipment for daily information (BP, HR, symptoms and weight);[13] likewise, the REM-HF[14,15] trial using a similar approach was also negative.

Weight may not be a specific enough marker of ADHF, since it may vary for many reasons. It is possible that current markers such as symptoms and weight gain are late and indirect measures of decompensation and that earlier detection of congestion could prompt interventions and avert the incoming ADHF and hospital admission.[15] Monitoring of intrathoracic impedance (Optivol® CRT-D), with an imbedded feature in some of the implanted devices (pacemaker or defibrillator) showed promise, but the DOT-HF study using intrathoracic impedance with an audible alert did not improve outcomes and increased HF admissions,[16] while the recent Multisense trial was negative.[17] Likewise neutral results were observed in stable patients using electronic implanted devices from multiple providers.[14]

Using more sensitive physiologic markers for the development of acute decompensation, such as increased filling pressure, may be beneficial. A variety of implantable hemodynamic monitors (IHM) have been developed to provide objective and continuous information on hemodynamic status in ambulatory HF patients, which may facilitate the timeliness of interventions and improve outcomes.[18] Interesting initial results were obtained for a pacemaker-like device with a RV lead that contains a sensor near its tip to measure right ventricle (RV) pressures (estimated pulmonary artery diastolic (ePAD)) in 274 patients enrolled in the COMPASS HF trial (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of HF).[19] Safety (8% complications, mostly lead dislodgements) and primary efficacy (21% decreased in HF-related events) endpoints were met. Unfortunately, the REDUCE-HF trial (REducing Decompensation events Utilizing intraCardiac prEssures in patients with cHF) was prematurely terminated due to sensor lead failure after 400 patients were enrolled and showed no significant difference in HF events after one year of follow-up.[19] Another device, the Heart-POD (Abbott Laboratories, Illinois, USA) measures directly the left atrial pressure and has shown promising results in a preliminary observational study of 40 ambulatory HF patients.[20] In order to try to further empower the patients in

HOMEOSTASIS, they followed a physician-directed therapeutic strategy guided by left atrial pressure (LAP), which led to a drop in mean daily LAP, decreased the HF hospitalization rate, and resulted in improvements in New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF) and pharmacological profiles.[20,21] A larger unblinded study, the LAPTOP-HF trial,[22,23] was recently stopped early due to excess of procedure related complications after enrolment of 486 of the 730 planned patients; the annualized HF hospitalization rates for implanted patients was 0.40 versus 0.68 in Control patients, RRR 41%, p=0.005, offering insights into the benefits of hemodynamic monitoring and the use of physician directed, patient self-management.[22,23] The patient self-management features have been embedded in a smart phone application that will be available commercially before the end of 2019 and that we propose to use for this protocol.

Recently the FDA and Health Canada approved a novel implantable sensor inserted into the right pulmonary artery that measures pulmonary artery pressures (PAP) in patients with HF, the CardioMEMS™ HF System (Abbott Laboratories, Illinois, USA). The coil and capacitor are housed within the sensor to form a miniature electrical circuit that resonates at a specific frequency; variation in PAP will alter the baseline resonant frequency emitted by the sensor, which is electromagnetically coupled to an external antenna for data transmission. Frequency shifts are displayed as pressure waveforms. The data can then be transmitted to the web-based platform for clinical analysis.[24] The CHAMPION trial evaluated the effect of PAP-guided therapy on HF-related hospitalizations compared to standard of care in 550 patients with NYHA functional class III or IV symptoms. A 28% reduction in HF-related hospitalizations was observed after 6-months of follow-up.[25] As expected, the presence of PH identified HF patients at risk for adverse outcomes, but knowledge of hemodynamic variables allowed for more effective treatment strategies to reduce hospitalizations, albeit with no impact on mortality.[26] Interestingly, both patients with HF with preserved ejection fraction (HFpEF) (using a definition of LVEF≥40%) and HF with reduced ejection fraction (HFrEF) derived benefit,[27] making the CardioMEMS™ HF System the first treatment option to show promise for patients with HFpEF, an increasingly recognized cause of group 2 PH.[28] Moreover, patients with chronic obstructive pulmonary disease (COPD) concomitant with HF also derived benefit from hemodynamic monitoring in CHAMPION.[29] An example of the proposed treatment algorithm is available at the

Annex 1.

Further, data from CHAMPION have shown that PH is underestimated by right heart catheterization (RHC) in nearly 50% of patients with HF.[30] RHC provides a "snapshot" of a patient's hemodynamic profile at a single time point, in a hospital-based setting, which may not reflect real life hemodynamics in other settings. These results are consistent with the ESCAPE trial in ADHF patients, which found that pulmonary artery (PA) catheter–guided care was not superior to traditional clinical assessment of volume in preventing subsequent decompensation.[31] However, levels of certain hemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) and mean PA pressure were predictors of later risk for hospitalization. Full characterization of PH status and guidance for medical management may be best accomplished with recurrent assessment of pressures provided by an implanted hemodynamic monitor (IHM). In CHAMPION, patients with no PH on RHC but PH revealed by the IHM had significantly higher HF hospitalization rates than those without this "occult" PH,[30] suggesting that IHM can provide additional information on the patient's overall risk of HF hospitalization. Further, the use of an IHM such as the CardioMEMS™ HF System provides an unique opportunity to fine-tune patient management with its dual capacity of providing daily information on congestion (diastolic PAP) and the severity of PH (systolic and mean PAP).

Lastly, there is increasing evidence that filling pressures may influence the arrhythmia burden; a positive relationship has been demonstrated between changes in intra-cardiac pressures and risk for ventricular tachycardia/ventricular fibrillation (VT/VF).[32] There are several potential mechanisms by which an elevated ventricular pressure could influence the development of arrhythmias: stimulation of neurohormonal activation,[33] increase in sympathetic tone,[34] and aberrant intracellular calcium cycling. In addition, acute diastolic stretch shortens action potential duration and refractoriness, whereas chronic dilatation does not,[35] presumably because of activation of stretch-activated channels.[36] There is an opportunity to evaluate the arrhythmia burden in patients with IHM, including atrial fibrillation (AF), VT/VF and implantable cardioverter defibrillator (ICD) events.

The possibility of remote HF monitoring with the CardioMEMS™ HF System opens a new avenue for patients with HF, especially the elderly or those living far away from HF clinics. The use of such high-intensity remote monitoring carries the potential for successful detection of parameter

deviations, tailored therapy, more rigorous follow-up and improved outcomes. Moreover, it has been shown to be cost-effective not only in CHAMPION[36] but also in a real life setting,[4] mostly because of reduction in hospital readmissions.[37]

At the Montreal Heart Institute (MHI), during the financial year 2018-19 there were 900 hospital admissions with a primary diagnosis of heart failure in 716 patients. Of those, 34% were readmitted within the same financial year and 241 patients had ≥1 readmission (range: 1-9) (see appendix 2). Targeting these high-risk patients with technology using pulmonary artery pressure monitoring could possibly expand our ability at the HFC to treat a larger number of patients remotely, decrease costly hospital readmissions and hence create a virtual heart failure disease management program (HFDMP).

Accordingly, we propose a paradigm shift towards disease co-management, using patient remote hemodynamic data, accessed through a smart phone app, and a virtual HF clinic run by a nurse clinician specialized in HF with the backup of a HF cardiologist.

2. HYPOTHESIS:

2.1 Primary Hypothesis

Due to the dynamic nature of HF and knowledge that filling pressures can rise rapidly over hours to days,[20] the capacity of patients to get precise PAP measurements as needed will provide critical information in a timely manner. Using a personalized strategy will allow for appropriate adjustments of medications based on current PAP values categorized and accessed via a smartphone app, which will help curtail increases in left-sided filling pressures and thereby avert hospitalizations for ADHF. Also providing the patient and nurse clinician access to the patients' hemodynamic data on a continuous basis could empower patients to take more responsibility in the management of their disease through engagement and self-learning concerning dietary indiscretion, fluid and salt restriction that may impact PAP measures. Finally, knowledge of their PAP may provide reassurance in the event of vague symptoms not directly attributable to HF and decrease the number of emergency department visits. It may also help in making non-HF diagnoses by eliminating HF as a cause of dyspnea (i.e bronchitis).

3. STUDY OBJECTIVES

To demonstrate that a virtual Heart Failure Clinic (HFC) based on patient self-management using PAP remote monitoring is superior to usual care of HFC, leads to decreased: hospital admission for HF, emergency department consultation and/or unplanned intravenous heart failure therapy and cardiovascular death, compared to a regular HF clinic, has low device-related complications and is cost-effective, in NYHA class III and II (requiring diuretics) patients.

4. STUDY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the time to first occurrence of any component of the composite event as adjudicated by the Clinical Event Committee (CEC). Components of the event are: acute decompensated heart failure that requires emergency department consultation and/or unplanned intravenous heart failure therapy in an outpatient clinic, or hospital admission for heart failure, or cardiovascular (CV) death during 12 months of follow-up.

4.2 Secondary Endpoints

4.2.1 Time to the first occurrence of the individual components of the composite endpoint

- Acute decompensated heart failure that requires emergency department consultation and/or unplanned intravenous heart failure therapy in an outpatient clinic;
- Hospital admission for heart failure;
- CV death

4.2.2 Changes in functional capacity between baseline and 12-months

- NYHA functional class;
- Quality of life (Kansas city cardiomyopathy (KCCQ) questionnaire) ;
- 6 minute walk distance.

4.2.3 Device-related endpoints (for CardioMEMS group only)

- Safety: adverse events related to the device;
- Number of successful patient contacts (virtual and clinic);
- PA pressures: changes, frequency of elevated readings;
- Ease of application utilization.

4.2.4 Cost-effectiveness

A cost utility analysis will be undertaken as part of the study protocol to evaluate the impact of the treatment strategy of remote PAP monitoring compared to usual care. An incremental cost-effectiveness ratio (ICER) will be calculated by comparison of calculated costs and quality-adjusted life years in both study groups. This data will then be used to construct an economic model to evaluate the cost-effectiveness in a hypothetical cohort of 10,000 patients. This data will be used to calculate the incremental cost per Quality-Adjusted Life Year (QALY) gained and per life-year gained. We will perform deterministic sensitivity analyses to explore the impact of uncertainty in key parameters on the analysis results and a probabilistic sensitivity analysis to further characterize uncertainty in model parameters.

Detailed resource utilization and costs will be collected prospectively for randomized patients, including diagnostic evaluation costs directly incurred as a result of the CardioMEMS™ HF System procedure, procedural costs, and inpatient treatment costs at a large tertiary care hospital in Montreal (MHI). Individual patient-level costs of heart failure hospitalizations, emergency room (ER) visits, and short stay costs for intravenous diuretics will be obtained from the Montreal Heart Institute. Follow-up costs will include protocol driven visits and tests, and additional unscheduled outpatient treatment visits for heart failure or visits to the HFC.

Evaluation of quality of life will be performed using the KCCQ questionnaire and quality adjusted life years (life expectancy adjusted for quality of life of the health state experienced) will be calculated for each patient in the alive state using published health utilities, which measure quality of life from a 0 (dead) to 1 (perfect health) scale, for heart failure according to NYHA Class and results of the KCCQ questionnaire. In the absence of questionnaire data for hospitalized patients, utility decrements will be applied for heart failure hospitalizations and emergency room visits as per the published literature. A short-term utility decrements (i.e. disutility) for the CardioMEMS™ procedure will be approximated using published decrements for percutaneous coronary intervention (PCI).

4.3 Tertiary/Exploratory Endpoints

4.3.1 Goal for best practice

- % achieved target dose of Guidelines-derived medical therapy (GDMT) (HFrEF);
- Medication changes (mean dose achieved by class of GDMT) between baseline and 12 months;
- Time (days) to achieve target doses of GDMT (HFrEF).

4.3.2 Changes in echocardiographic parameters between baseline and 12 months

- Cardiac remodeling including left ventricle (LV) end-systolic and end-diastolic volumes indexed to blood surface area (BSA), LVEF, RV dimensions and function including RV-PA coupling, left atrium (LA) volume, mitral and tricuspid regurgitation severity, with a complete echocardiography protocol proposal and Core Laboratory analysis.

4.3.3 Changes in biomarkers levels between baseline and 12-months

- Blood samples will be collected for biomarkers analysis: General (Electrolytes, BUN, creatinine and CBC), and disease-specific (HS-CRP, NT-proBNP, troponin, Osteopontin, Angiotensin-II, aldosterone, ST2, Vasopressin, galectin-3, PIIINP, cystatin C).

4.3.4 Arrhythmia Burden

- Episodes of atrial fibrillation requiring medical attention (ED visits or hospitalization);
- VT/VF events;
- Anti-tachycardia pacing or appropriate ICD shocks in patients with an ICD

4.3.5 Patient quality of life and satisfaction

- Regarding both the virtual follow-up itself and the personalized algorithm using the application. Standardized quality of life questionnaires will be used.

4.3.6 Drug concentrations

- Blood samples will be collected to measure concentrations of drugs commonly used in HF patients at the baseline visit, as well as at visits at week 2, month 2, month 12 and at unscheduled visits.

5. STUDY PROTOCOL

5.1 Study design

***Type of study**:* A single center prospective randomized open-label blinded-endpoint (PROBE) trial is proposed comparing two strategies for patients with HF who had at least one admission for a primary diagnosis of HF regardless of LVEF in the previous year i.e., usual care by a specialized multidisciplinary HF clinic team versus hemodynamic monitoring and self-empowered remote follow-up using the newly developed smart-phone/iPad application, with the back-up of a nurse clinician and a HF cardiologist and limited HF clinic visits.

150 eligible patients who consent to participate will be randomized to the control group or intervention group in a 1:1 ratio. Patients randomized to hemodynamic monitoring (CardioMEMS group) will have the CardioMEMS™ HF System implanted as an outpatient procedure within a week of random assignment.
Before randomization, patients will need to be stable as judged by the treating HF clinic cardiologist. After randomization, all subjects will receive education on HF as per local practice as well as recommendations regarding nutrition and exercise, for daily weights, medication record, clinical notes and appointments.

Patients in the control group will be followed as per usual practice by the MHI multidisciplinary HF clinic. Patients in the CardioMEMS group will be seen at baseline, week 1 and week 2 after implantation, two months and twelve months after randomization and will be in regular contact with the lead research nurse with virtual follow-ups at weeks 3, 4, 6, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. The specialized HF clinician nurse and cardiologist will design an individualized pre-specified therapeutic plan according to CHF guidelines and clinical experience with that individual patient (Appendix 3). For HFrEF, GDMT will be implemented in both groups, including ICD and CRT referral when indicated.

For patients in the CardioMEMS group, a blood pressure cuff will be provided and hemodynamic data will be taken twice daily by the patient from the moment of randomization in the trial. i-Pad® internet communication using Skype/Facetime or telephone calls will be done twice in the first month, once in the second month and monthly thereafter, unless a medical problem occurs that

requires more frequent contact, which will be determined by the study team. The patient will implement the individualized therapeutic plan designed by the HF clinician nurse and cardiologist, following a pre-specified algorithm (Appendix 1), which includes titration of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), hydralazine, nitrates, beta-blockers and mineralocorticoid antagonists as needed. Initiation of some of these medications may require a visit to the research clinic, if judged necessary and will be counted as unscheduled visit. Diuretics and potassium supplementation will be adjusted according to individualized target PAP pressures, electrolytes and renal function. Blood samples for electrolytes and renal function: sodium, potassium, chloride, and bicarbonate will be drawn one week after any changes of medications, or as deemed clinically indicated by the treating team. The research team will follow the laboratory results and intervene as needed. Objectives for PAP pressures will be similar to the CHAMPION trial, i.e., PAP systolic (15–35 mmHg), PAP diastolic (8–20 mmHg), and PAP mean (10–25 mmHg). PA measurements will be transmitted daily for the first two weeks, three times a week thereafter, and more frequently as needed. Also, patients will have access to the research nurse coordinator for advices or to signal changes in their state (for example a bronchial infection, diarrhea etc.). Further, patients in the CardioMEMS™ group will have access to categorized data (very low, low, in range, high or very high pressures) using the app and be able to adjust their medication (mostly diuretics) according to an individualized algorithm. Furthermore, data reaching thresholds will be reviewed daily during working days and patients will be contacted in the event of clinically significant changes, as individually defined at the outset. The general aim is to introduce and rapidly up-titrate GDMT for patients with HFrEF (ACEi, ARB or ARNI), beta-blockers and mineralocorticoid receptor antagonists (MRA), to reduce or eliminate diuretic doses for patients with low or very low PAP, and to increase diuretic or vasodilator doses for high or very high PAP. A general algorithm is proposed in Appendix 1.

5.2 Inclusion/Exclusion Criteria

5.2.1 Inclusion Criteria

1. Male or female ≥ 18 years old.
2. Symptomatic HF (NYHA III) with recent heart failure admission in the previous year (12 months). OR

3. Patient with at least one ER visit or unplanned HF clinic requiring iv diuretics within 12 months will be eligible if they have in addition a N-terminal pro-BNP (NT-proBNP) level > 800pg/ml at screening AND NYHA Class II on diuretics (furosemide ≥ 40mg qd), III or ambulatory IV.
4. HF with reduced or preserved EF of at least 3 months duration.
5. Minimum technological knowledge either with a smartphone or iPAD for use of the self-management application, including access to internet.
6. Anatomical criteria
    a. PA branch diameter between 7 mm – 15 mm
    b. For BMI >35, distance from patient's back to target PA<10cm

5.2.2 Exclusion Criteria

In order to maximize the generalizability of the results, exclusion criteria will be kept to a minimum:

1. ***Recent cardiovascular event*:** Acute coronary syndrome (STEMI/NSTEMI; a small rise in the troponin level would be expected in this population and is not a contraindication for enrolment); Percutaneous Coronary Intervention (PCI), new cardiac rhythm management (CRM) device (pacemaker, ICD and CRT), CRM system revision, lead extraction or cardiac or other major surgery or transient ischemic attack or stroke within 2 months (3 months of stabilization after CRT or cardiac surgery);
2. Scheduled cardiac surgery;
3. History of pulmonary embolism or recurrent deep vein thrombosis;
4. Persistent NYHA Class IV and ACC/AHA HF Stage D, patients implanted with a ventricular assist device (VAD), or patients listed for cardiac transplantation and likely to be transplanted within 12 months;
5. Coexisting severe stenotic valve lesions, endocarditis, obstructive hypertrophic cardiomyopathy, acute myocarditis, tamponade, or large pericardial effusion;
6. Clinically too unstable to be followed remotely; this includes but is not limited to:
    a. Resting systolic blood pressure < 80 or > 180 mmHg;
    b. Resting heart rate > 100 bpm;

c. Stage IV or V chronic kidney disease (Estimated Glomerular Filtration Rate (eGFR) that remains < 30 mL/min/1.73m^2 by MDRD) or nonresponsive to diuretic therapy or on chronic renal dialysis;

7. Severe pulmonary hypertension with systolic pulmonary artery pressure ≥80 mmHg;
8. Pulmonary hypertension other than group II PH;
9. Anemia requiring transfusions, iron infusions, or hemoglobin below 100;
10. Coagulopathy or uninterruptible anticoagulation therapy or contraindication to antiplatelet/anticoagulant treatments anticipated in the protocol;
11. Intolerance to aspirin or clopidogrel;
12. Active infection requiring systemic antibiotics;
13. Unwillingness to sign informed consent or to attend the outpatient clinic;
14. Participation in another research trial with intervention;
15. Discharge to a chronic care facility or residence in an outlying area;
16. Pregnant or lactating women or women of childbearing potential who are not protected from pregnancy by an accepted method of contraception, such as the oral contraceptive pill, an intrauterine device or surgical sterilization. If necessary a negative urine or blood test will be performed before randomization
17. Any condition that in the opinion of the investigator would jeopardize the evaluation for efficacy or safety or be associated with poor adherence to the protocol, including cognitive decline.
18. Life expectancy <1 year;

5.3 Subject Attribution Number

Once informed consent is obtained, each subject will be assigned a unique 3-digit subject identification (SID) number ("Subject number") for unambiguous identification throughout the study; it will be constructed as follows:

3 Digits: Subject number, unique within the study center starting at 001.

Sequential numbers will reflect the order in which subjects are recruited. SID numbers will be used in sequence with no number skipped, substituted, or re-used.

6. SUBJECT EVALUATION

6.1 Informed Consent

Before any screening examination takes place, potentially eligible subjects will be given a full explanation as to what the study entails. This will be performed verbally and in writing. Subjects will be given ample time to consider participation and pose any questions they may have. Subjects who are willing to take part in the study will then be asked to sign an informed consent form. Screening examinations will only be performed after written informed consent is obtained. Subjects who continue to meet enrolment criteria upon completion of the screening process will be eligible for randomization.

6.2 Visits

At Baseline visit the consent form will be signed and inclusion and exclusion criteria will be reviewed before randomization. Only Baseline and Final Visits will be scheduled in the study for the Control Group. All other visits will be scheduled according to usual care by the treating HF clinic team.

Baseline visit (Visit 1)

- Informed Consent
- Allocation of unique SID number
- Demographic information: demographic data and other population characteristics including sex, race, year of birth, age, smoking history, and alcohol consumption
- Medical and surgical cardiovascular history (including cardiovascular risk factors)
- NYHA Class
- Physical examination by physician
- Vital signs in sitting position (blood pressure (BP) and heart rate (HR)) after resting for at least 5 min, 2 measurements, 2 minutes apart
- Weight, height
- Echocardiography
- 12-lead ECG in supine position, after resting for at least 5 min.
- Assessment of eligibility criteria
- Randomization to study group

- Current therapy and timing
- Subject education: nutrition, exercise, education regarding HF
- Blood tests
  - BUN, Creatinine, Electrolytes, CBC, NT-proBNP
  - Blood samples for subsequent analysis: Cystatin-C, Angiotensin-II, Aldosterone, Vasopressin, hS-CRP, ST2, Galectin-3, Troponin, Osteopontin, PIIINP, drug concentrations.
- Urine or blood pregnancy test for women of childbearing potential
- 6-minute walk test
- Quality of Life Questionnaire (MLHF)

For patients randomized to CardioMEMS:

Implantation Visit (visit 2)

- CardioMEMS Implantation
- Hemodynamic data collection
- Assessment of AEs/SAEs

Week 1 after implantation (Visit 3)

- Adjustment of medication
- Subject technology training
- Assessment of AEs/SAEs

Week 2 after implantation (Visit 4)

- NYHA Class
- Physical examination by physician
- Vital signs in sitting position (blood pressure (BP) and heart rate (HR)) after resting for at least 5 min, 2 measurements, 2 min apart
- Weight
- Current therapy and timing
- Adjustment of medication
- Lab Assessment : BUN, Creatinine, Electrolytes, CBC, NT-ProBNP

- Blood sample for drug concentrations
- Assessment of AEs/SAEs

Month 2 (Visit 5)

- NYHA Class
- Physical examination by physician
- Vital signs in sitting position (blood pressure (BP) and heart rate (HR)) after resting for at least 5 min, 2 measurements, 2 min apart
- Weight
- Current therapy and timing
- Adjustment of medication
- Lab Assessment: BUN, Creatinine, Electrolytes, CBC, NT-proBNP
- Blood sample for drug concentrations
- Assessment of AEs/SAEs

Virtual Visits

Virtual visits will be done remotely (patient self-management using PAP monitoring) following hospital discharge of the implant: week, 3, 4, 6, 12, 16, 20, 24, 28, ..., 48

- Current therapy
- Adjustment of medication
- Remote evaluation by nurse: HF symptoms
- Remote hemodynamic evaluation by nurse
- Laboratory assessment (if clinically indicated 1 week after change in medication dosage)
- Assessment of AEs/SAEs

For all randomized patients:

Unscheduled Visit(s)

- NYHA Class
- Physical examination by physician
- Vital signs in sitting position (blood pressure (BP) and heart rate (HR)) after resting for at least 5 min, 2 measurements, 2 min apart

- Weight
- 12-lead ECG (if indicated).
- Current therapy and timing
- Adjustment of medication
- Blood tests
  - BUN, Creatinine, Electrolytes, CBC, NT-proBNP
- Blood samples for drug concentrations
- Assessment of AEs/SAEs

Month 12 (Final Visit 6)

- NYHA Class
- Changes in medical and surgical cardiovascular history
- Physical examination by physician
- Vital signs in sitting position (blood pressure (BP) and heart rate (HR)) after resting for at least 5 min, 2 measurements, 2 min apart
- Weight
- Echocardiography
- 12-lead ECG in supine position, after resting for at least 5 min.
- Current therapy and timing
- Blood tests: BUN, Creatinine, Electrolytes, CBC, NT-proBNP
- Blood samples for subsequent Analysis: Cystatin-C, Angiotensin-II, Aldosterone, Vasopressin, hs-CRP, ST2, Galectin-3, Troponin, Osteopontin, PIIINP, drug concentrations.
- 6 minute walk test
- Quality of Life Questionnaire (MLHF)
- Assessment of AEs/SAEs

End of study visit:

Every implanted participant will be followed at the Heart Failure Clinic at the end of the trail within one month of study termination.

7. FLOW CHART

	CardioMEMS and CONTROL GROUPS							
Group	**Both Groups**	**CardioMEMS Group Only**						**Both Groups**
Visit (V)	**Baseline Randomization** Visit 1	**Implantation** Visit 2	**Week 1 post implantation** Visit 3	**Week 2 post implantation** Visit 4	**Month 2** [5] Visit 5	**Virtual** [5] Week 3, 4, 6,12, 16 20,24,28,….,48	**Unscheduled**	**Month 12** [5] Final visit Visit 6
Visit Windows (days)	0	≤7	±4	±4	±14	±4		±14
Informed Consent Form	X							
Demographics	X							
Medical & Surgical CV History	X							X[6]
NYHA Class	X			X	X		X	X
Physical Exam by physician	X			X	X		X	X
Vital Signs	X			X	X		X	X
Weight	X			X	X		X	X
Height	X							
Echocardiography	X							X
ECG	X						X [3]	X
Inclusion/Exclusion criteria	X							
Randomization to Study Group	X							
Current Therapy and timing	X			X	X	X	X	X
Adjustment of Medication			X	X	X	X	X	X
Subject Education (Nutrition, exercice etc.)	X							
CardioMEMS Device		X						
Subject Technology Training			X					
Remote evaluation by nurse: HF symptoms						X		
Remote hemodynamic Evaluation by nurse:						X		
Hemodynamic Data Collection		X						
Laboratory Assessment: *Electrolytes, Creatinine, CBC, Urea, NT-proBNP*	X			X	X		X	X
Laboratory Assessment (Virtual Visit):						X [4]		
Blood sample for subsequent analysis: *Cystatin C, Angiotensin-II, Aldosterone, Vasopressin, HS-CRP, Galectin-3, Troponin. Osteopontin, ST2, PIIINP*	X							X
Urine Pregnancy Test	X[1]							
Drug concentrations	X			X	X		X	X
6 min walk test	X							X
Quality of Life Questionnaire (KCCQ)[2]	X							X
Assessment of AEs/SAEs		X	X	X	X	X	X	X

[1] For women of childbearing potential [3] If indicated [5] Post baseline visit [6] Change(s) in Med & Surgical CV History
[2] Kansas City Cardiomyopathy Questionnaire [4] No Blood test except by local lab if clinically indicated (1 week after change in medication dosage)

7. SPECIFIC ASSESSMENTS

7.1 End point variables

Blood pressure measurement, biochemistry monitoring and renal function

Blood pressure will be measured and recorded at each visits according to the recommendations of the Canadian Hypertension Education Program.[38] Electrolytes, serum creatinine and vital signs will be assessed as described in the Study flow chart. In the assessment renal function, eGFR will be calculated as previously described using the MDRD equation.[39]

Cystatin C

Moreover, in order to better characterize changes in renal function during the study, cystatin C will be measured at baseline and at the end of the study. Cystatin C is a novel biomarker of renal function which appears to be more sensitive than serum creatinine to detect modest changes in renal function.[40]Moreover, in HF, it has been shown to be a powerful prognostic marker.[40]

N-terminal proB-type natriuretic peptide (NT-proBNP).

BNP is secreted primarily from the ventricles in both healthy individuals and patients with CHF.[41] The production of BNP in the ventricle increases proportionally with increases in both ventricular wall tension and stretch. Both BNP and NT pro-BNP, the inactive portion of pro-BNP, have been shown to correlate with LVEF, left ventricular volumes and pressures. While neurohumoral blockade decrease the NT-proBNP levels and prognosis, to our knowledge, there has been no study showing that effective pressure management significantly reduce concentrations of BNP and NT-proBNP. NT-proBNP will be measured by Dr. Joel Lavoie using the « Roche proBNP assay » (Roche Diagnostics, Mannheim, Germany), on the Elecsys 2010 analyzer (Roche diagnostics). Our group has had extensive experience in measuring NT-proBNP in previous studies.[42-45]

PIIINP

It is now widely accepted that aldosterone induces deleterious effects on extracellular matrix balance, for which type I and III collagen constitute the majority of the collagen.[46-48] These alterations in collagens type I and III have been proposed to play a key role in myocardial stiffness.[48] Previous work has demonstrated that PIIINP serum levels were associated with poor outcomes in patients with HF.[49,50] Because it is expected that pressure management will reduce

myocardial stress in HF patients,[50-52] PIIINP will also be measured. PIIINP will be measured in the laboratory at the Montreal Heart Institute directed by Dr Martin G. Sirois using the Orion Diagnostica's UniQ PIIINP assay. The use of this assay has been validated in numerous studies in humans. Dr Sirois's laboratory has measured PIIINP in a study comparing circulating levels of various biomarkers between patients with systolic HF and HF-PEF, as well as in a study comparing concentrations of biomarkers between patients with HF and anemia and HF patients without anemia.[53] Together with NT-proBNP, this biomarker will be very important in demonstrating that the beneficial effects of pressure management on cardiac remodeling.

Osteopontin (OPN)

An additional marker of remodeling, osteopontin [OPN]) is a glycoprotein that can be detected in plasma and was found to be upregulated in several animal models of cardiac failure[54] and may thus represent a new biomarker that facilitates risk stratification in patients with heart failure;[48] it has been shown to correlate with disease severity and poor prognosis.[55,56] OPN seems to have a pivotal role in the development of Angiotensin II-induced cardiac fibrosis and remodeling. Moreover, the effect of Eplerenone on the prevention of cardiac fibrosis, but not cardiac hypertrophy, might be partially mediated through the inhibition of OPN expression.[57] Thus, we will also measure angiotensin-II and aldosterone, two important steps in the remodeling and fibrosis pathways.

High sensitivity C-Reactive protein (HS-CRP)

While heart failure has been shown to be an inflammatory condition,[58,59] the impact of pressure management on HS-CRP has not been well characterized. We herein propose to measure HS-CRP in our patients undergoing hemodynamic monitoring.

Cardiac Troponin T (cTnT)

In heart failure, the level of troponin correlates with prognostic independently of the presence of ischemic etiology or myocardial stretch assessed by NT-proBNP. This troponin leak varies with time and has been shown to be associated with decreased survival. We herein propose to measure cTnT in our patients undergoing hemodynamic monitoring.

Emerging markers

Galectin-3 serves important functions in numerous biological activities including cell growth, apoptosis, pre-mRNA splicing, differentiation, transformation, angiogenesis, inflammation, fibrosis and host defense.[60-63] Numerous previous studies have indicated that galectin-3 may be used as a diagnostic or prognostic biomarker for certain types of heart disease, kidney disease and cancer.[64] Galectin-3 levels are correlated with elevated risk for new HF in healthy people and acute myocardial infarction with reduced ejection fraction patients.[65] Thus, it is probable that galectin-3 has a more important role in the beginning stage of HF including early fibrosis and ventricular.[66] Whether hemodynamic management leads to improved levels of the biomarker is unknown at the present time.

ST2 cardiac **biomarker** is a protein biomarker of cardiac stress encoded by the **IL1RL1** gene. ST2 signals the presence and severity of adverse cardiac remodeling and tissue fibrosis, which occurs in response to myocardial infarction, acute coronary syndrome, or worsening heart failure.[62,67,68,59] ST2 provides prognostic information that is independent of other cardiac biomarkers such as BNP, NT-proBNP, highly sensitive troponin, GDF-15, and galectin-3.[3] One study indicated that discrimination is independent of age, body mass index, history of heart failure, anemia and impaired renal failure or sex.

Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH) is a peptide hormone formed in the hypothalamus, then transported via axons to the posterior pituitary, which releases it into the blood. AVP has two principle sites of action: the kidney and blood vessels.[69] The primary function of AVP in the body is to regulate extracellular fluid volume by regulating renal handling of water, although it is also a vasoconstrictor. AVP acts on renal collecting ducts via V_2 receptors to increase water permeability (cAMP-dependent mechanism), which leads to decreased urine formation (hence, the antidiuretic action of "antidiuretic hormone"). This increases blood volume, cardiac output and arterial pressure. Heart failure is associated with what might be viewed as a paradoxical increase in AVP. Increased blood volume and atrial pressure associated with heart failure should decrease AVP secretion, but it does not. It may be that sympathetic and renin-angiotensin system activation in heart failure override the volume and low pressure cardiovascular

receptors (as well as the hypothalamic control of AVP release) and cause an increase in AVP secretion.[70] Nevertheless, this increase in AVP during heart failure may contribute to the increase in systemic vascular resistance as well as the enhanced renal retention of fluid that accompanies heart failure. Whether hemodynamic monitoring leads to a decrease in AVP is unknown.

Drug concentrations

Concentrations of commonly used drugs in patients with HF will be measured at the baseline visit, as well as at visits at week 2, month 2, month 12 and at unscheduled visits. At each of these visits, the dose, the time of administration of the last dose of the cardiovascular medications and the time of the blood draw will be recorded.

Currently, very little information is available regarding the pharmacokinetic (PK) or concentrations of drugs in HF patients.[71] Data from our group and others have suggested marked differences in the concentrations or PK of commonly used drugs in HF patients compared to healthy individuals such as spironolactone and candesartan (manuscripts submitted). This could be attributable to several factors such as decreased renal function.[71] Moreover, only very limited data are available on the factors influencing the PK of drugs in patients with HF.[71]

In addition, little information is available on the magnitude of the effects of common dosing adjustments of HF drugs in "real-life" HF patients on drug concentrations, or whether patients who cannot reach target doses of HF medication actually have lower drug concentrations than those who do. Indeed, some patients who do not reach target doses could present comparable drug concentrations as patients reaching target doses, if they present clinical factors that predispose to increased concentrations, such as renal dysfunction.[71]

The screening and quantification of drugs or their active metabolites will be performed in plasma at the Platform of Biopharmacy of the Faculty of Pharmacy at Université de Montréal using Liquid Chromatography coupled to triple quadrupole mass spectrometer (LC-MS/MS) in the selective MRM mode[72-76] and Liquid Chromatography High-Resolution Mass Spectrometer (LC-HRMS) of the type quadrupole time-of-flight (QTof) in the full scan mode.[77-82] This group has an extensive experience for developing and optimising the bioanalytical techniques needed to measure

drugs/metabolites.[83-97] In addition to comparing drug concentrations between groups and concentrations changes, for drugs used in 30 or more patients, we will perform exploratory population-pharmacokinetics modelling. Modelling analyses will be performed by the STP2 Laboratory (Faculty of Pharmacy at Université de Montréal) using the gold standard for population pharmacokinetics modelling to estimate parameter and, interindividual and residual variability.[98,99] Population pharmacokinetics modelling will be done using nonlinear mixed effect modeling (NONMEM®, version 7.4, ICON Development Solutions). Pharmacokinetics studies in patients with special conditions are at the center of the STP2 Laboratory research.[100-108]

8. SAFETY

All Adverse events and serious adverse events will be reviewed by the investigator or a sub-investigator.

8.1. Definition of Adverse Events, Serious Adverse Events, and procedures for reporting Serious Adverse Event

8.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device and events related to the procedures involved.

8.1.2. Serious Adverse Event definition (SAE)

A serious adverse event is an AE that fulfills one or more of the following:

1. Results in death
2. Led to serious deterioration in heath of the subject, that either resulted in
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function, or
    - Requires in-patient hospitalization or prolongation of existing hospitalization

- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

3. Results to fetal distress, fetal death or a congenital abnormality/birth defect.

Note: Planned hospitalization for a pre-existing condition or a procedure is not considered a serious adverse event.

8.1.3. Adverse device Effect (ADE)

Adverse event related to the use of an investigational medical device.

Notes: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.1.4. Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

8.1.5. Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CardioMEMS user's Manual, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [41]

8.1.6. Procedures for Adverse Event reporting

8.1.6.1. Investigator Reporting

All AEs considered device related will be recorded in the eCRF for enrolled subjects.

Any Serious Adverse Event that occurs in the course of the study must be reported to Montreal Health Innovations Coordinating Center (MHICC) within one day of the investigator becoming aware of the SAE. All SAEs will be recorded in the electronic Case Report Form (eCRF) as adverse events up to 14 days after final visit. The investigator is responsible for informing the Ethics Committee of the SAE as per local requirements.

9. STATISTICAL ANALYSIS

Descriptive statistics of all study endpoints will be presented overall and broken down by group. Number of observations, mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Count and proportion will be displayed for categorical variables.

For the primary endpoint, the analysis will consist of an unadjusted comparison of time to first event. Event-rate curves will be estimated by the Kaplan-Meier product-limit method and the difference between groups will be assessed using the log-rank test. Components of the primary endpoint will be analyzed similarly.

ANCOVA models will be used to compare continuous endpoints expressed as change from baseline to 12 months between the standard group and the virtual group. The main model will include fixed effects for group with the baseline value as a covariate. Difference between groups in other continuous endpoints will be tested by either two-sample t-tests or Wilcoxon rank-sum tests depending on the normality of the data. Difference between groups in categorical endpoints will be tested using Chi-square tests.

Basic assumptions of the proposed analyses will be checked and data transformation or other analyses could be done if appropriate. For example, as some endpoints are likely to be skewed (ex. hs-CRP), log-transformation might be used, in which case descriptive statistics would also include geometric means. Missing values will not be imputed.

All statistical tests will be two-sided and conducted at the 0.05 significance level. Statistical analyses will be done using SAS version 9.4 or higher.

A statistical analysis plan (SAP) will be written to fully describe the statistical analyses that will be done. The SAP will be finalized prior to database lock.

9.1. Sample size

It is hypothesized that virtual monitoring will be superior to standard care in reducing the risk of the composite primary endpoint of acute decompensated heart failure that requires emergency department consultation and/or unplanned intravenous heart failure therapy in an outpatient clinic, hospital admission for heart failure, or CV death during 12 months of follow-up. The sample size rationale and assumptions are based on the following:

From the CHAMPION trial, the rate of HF hospitalization at 12 months was 0.52 and 0.75 in the treatment and control groups respectively (Phil Adamson personal communication, unpublished data), leading to a hazard ratio of 0.53. Similar event rates are expected for the primary endpoint in this trial. The mortality rate is expected to be similar between the two groups as in CHAMPION.

Using a log-rank test, a total of 136 subjects (68 in each group) would provide 80% power with a two-sided significance level of α=0.05. Factoring in a drop-out rate of approximately 10%, a total of 150 patients are required.

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval

The protocol and the informed consent document must have the initial and at least annual (when required) approval of an IRB/IEC. The signed IRB/IEC approval letter must identify the documents approved (i.e. list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Written information to be provided to the subject (i.e. patient cards, patient diary, instructional material on nutrition, exercise, and HF) and any advertisement used to recruit subjects must also be reviewed by the IRB/IEC.

10.2. Informed Consent

Regulatory agencies have issued regulations to provide protection for human subjects in clinical investigations and to describe the general requirements for informed consent. The informed consent document shall contain all the elements of informed consent specified in the application regulations. Some regulations may require the disclosure of additional information to the subject and/or inclusion of additional information in an informed consent document.

10.3. Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix 5) and that are consistent with good clinical practices (GCP) and the applicable requirements.

10.4. Case Report Form

All data will be recorded on eCRF provided by the MHICC.

10.5. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

11. DATA QUALITY ASSURANCE

The principal investigator performs quality control and assurance checks on all clinical studies that he/she performs. Before enrolling any subjects in this study, the principal investigator and study coordinator review the protocol and the eCRFs, determine the procedure for obtaining informed consent, and determine the procedure for reporting AEs and SAEs. The principal investigator or study coordinator reviews the data for accuracy and safety information. The principal investigator or study coordinator reviews the data for legibility, completeness and logical consistency.

11.1. Monitoring, Audits and inspections

In accordance with applicable regulations, GCP, and sponsor's / Academic Contract Research Organization's (ARO) procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor's designee will monitor the site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study procedures in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated ARO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the MHICC immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.2. Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The investigator's contract will contain all regulations relevant for the study center.

12. DATA MANAGEMENT

The MHICC will be the data coordinating center. The data collection tool for this study will be a validated electronic system. Subject data necessary for analysis and reporting will be entered into database or data system. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. laboratory).

13. TRIAL COMMITTEES

13.1. Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established. The CEC will consist of physicians who have no affiliation with the CardioMEMS™ HF System trial, are not employees

of Abbott Laboratories, or have no significant investment in Abbott Laboratories or their entities. This committee will be composed of at least 3 members from which at least two are HF cardiologists. Events for adjudication will include primary endpoints and device or procedure related adverse events. Criteria for adjudication, procedures, data flow will be described in separate CEC charter generated and maintained by the MHICC.

13.2. Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be established. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety of study procedures and for monitoring the overall conduct of the study The DSMB will consist of three experienced physicians with expertise in clinical trial conduct. The DSMB will meet by teleconference once a year, with additional meetings or conference calls scheduled as needed.

Proposed Table 1. Patient Characteristics at Enrollment

	Standard care	Virtual clinic	p value
Demographics and clinical			
Age,			
Gender			
Weight			
Body Mass Index (BMI)			
NYHA class, median (range)			
Heart rate, bpm			
Systolic blood pressure, mmHg			
Diastolic blood pressure, mmHg			
Medical History			
Dyslipidemia, %			
Diabetes mellitus, %			
Hypertension, %			
Aetiology of HF, % ischemic			
Prior myocardial infarction, %			
CABG, %			
Percutaneous coronary intervention, %			
Stroke			
Atrial fibrillation, %			
Sustained Ventricular Arrhythmias, %			
CRT, %			
ICD, %			
Pacemaker, %			
Medications			
ACEi/ARB, %			
ARNi, %			
B-blockers, %			
MRA, %			
Ivabradine, %			
Digoxin, %			
Hydralazine/nitrates, %			
Loop diuretics, %			
Other diuretics, %			
Laboratory testing[#]			
Sodium, mmol/l			
NT-proBNP, pg/mL			
BUN, mmol/L			
eGFR, mL/min/1.73 m2 (MDRD)			
Hemoglobin			

6-Minute walk, m			
Echocardiography[#]			
LVEF, %			
% with HFPEF (LVEF>40%)			
LVESVI, ml			
LAVi, ml			
RV TAPSE			
ePAPSP			
PVR, Wood units			
Resting hemodynamics[&]			
RAP, mean, mm Hg			
PAP, systolic, mm Hg			
PAP, diastolic, mm Hg			
PCWP, mm Hg			
Cardiac output, L/min			
Cardiac index, L /min/m2			
SVRI, dyne/ s/cm/m2			
PVR, Wood units			
RVSWI, mL/beat/m2			

Selected parameters presented here; Data will likely be presented for HFrEF and HFpEF.
& in implanted patients only.

NYHA indicates New York Heart Association; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVESVI: LV end systolic volume indexed to BSA; LAVi: Left atrial volume indexed to BSA; RV TAPSE: RV tricuspid annular plane systolic excursion, using Tissue Doppler imaging; eSPAP: estimated systolic PAP; PVR, pulmonary vascular resistance; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance; and RVSWI, RV stroke work index.

Data will be summarized as mean±SD (range) unless otherwise specified.

Proposed Table 2. Changes in the main Parameters between baseline and 12-months in Survivors

	Standard care	Virtual clinic	p value
Clinical			
NYHA class, median (range)			
Heart rate, bpm			
Systolic blood pressure, mmHg			
6-Minute walk, m			
MLHFQ			
Laboratory testing[#]			
Sodium, mmol/l			
NT-proBNP, pg/mL			
BUN, mmol/L			
eGFR, mL/min/1.73 m2 (MDRD)			
Hemoglobin			
Hs-CRP			
Troponin			
Osteopontin			
Angiotensin-2			
Aldosterone			
Vasopressin			
PIIINP			
Galectin-3			
ST2			
Cystatin C			
Echocardiography[#]			
LVEF, %			
% with HFPEF (LVEF>40%)			
LVESVI, ml			
LAVi, ml			
RV TAPSE			
ePAPSP			
PVR, Wood units			

*Frailty index using the Fried scale[40]; # Selected parameters; final table will vary according to findings; & in implanted patients only.

NYHA indicates New York Heart Association; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVESVI: LV end systolic volume indexed to BSA; LAVi: Left atrial volume indexed to BSA; RV TAPSE: RV tricuspid annular plane systolic excursion, using Tissue Doppler imaging; eSPAP: estimated systolic PAP; PVR, pulmonary vascular resistance; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance; and RVSWI, RV stroke work index. Data will be summarized as mean±SD (range) unless otherwise specified. p values will be for comparisons across all time points.

Proposed Table 3. Pharmacological Profiles and Goal for best practice at 12 months

	Standard care			Virtual clinic			p values
MEDICATION	**All**	**HFrEF**	**HFpEF**	**All**	**HFrEF**	**HFpEF**	
ACE or ARB, % and mean dose							
% achieved target dose			NA			NA	
ARNi, % and mean dose							
% achieved target dose						NA	
β-blocker, % and mean dose							
% achieved target dose			NA			NA	
Mineralocorticoid receptors antagonist, % and mean dose							
% achieved target dose							
Ivabradine, % and mean dose							
% achieved target dose							
Loop diuretic, % and mean dose							
Thiazide diuretic, % and mean dose							
Digoxin, % and mean dose							
Long-acting nitrates, % and mean dose							
Hydralazine, % and mean dose							
MEDICATION CHANGES							
Number of medication changes/patient, mean, range							
time (days) to achieve target doses of GDMT							

**P* for comparison between baseline and 12 months

Proposed Table 4: Device related endpoints

- Safety: adverse events related to the device;
- number of successful patient contacts (virtual and clinic);
- PA pressures: changes, frequency of elevated readings

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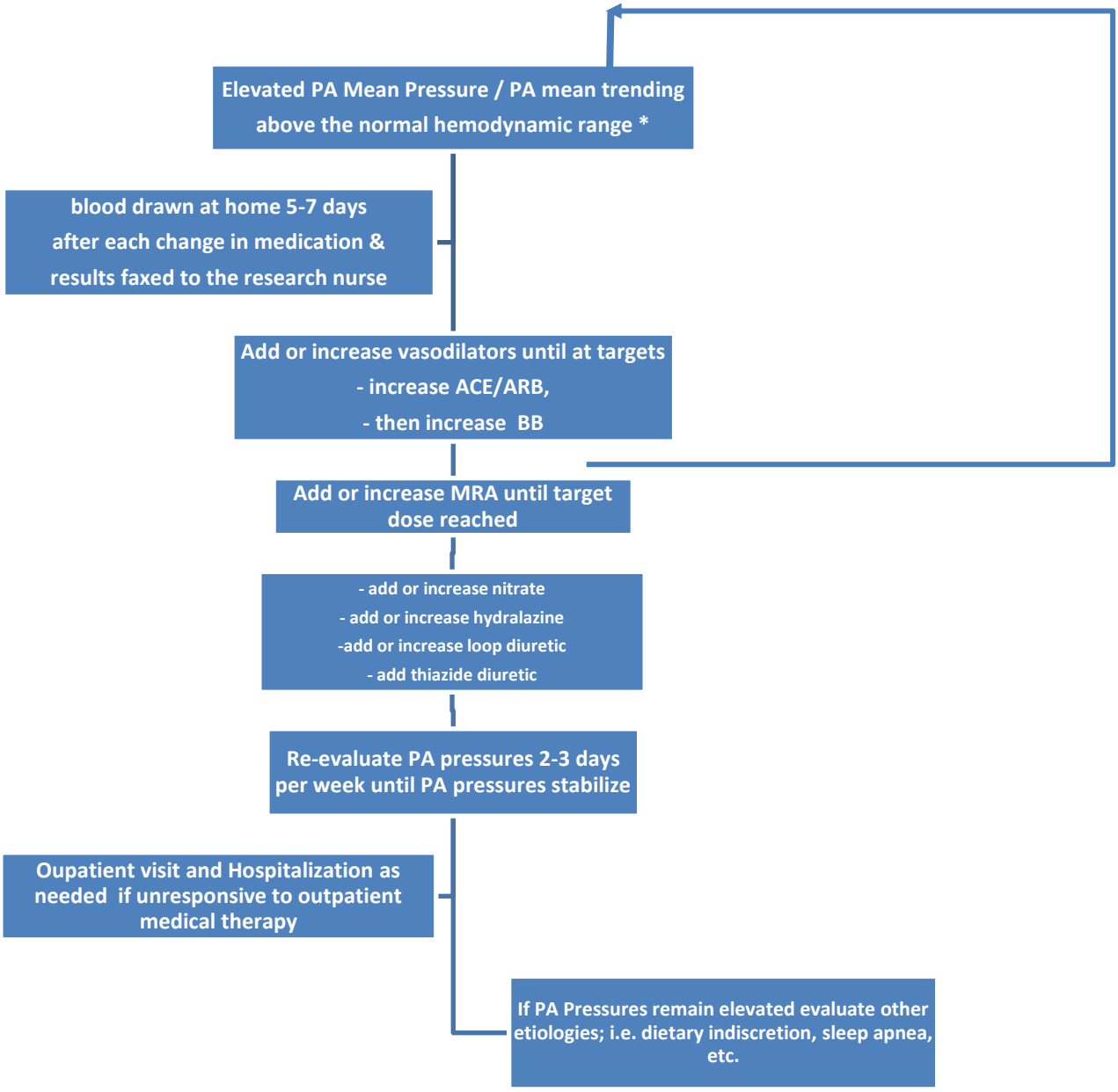
Appendix 1: Elevated PA Mean Pressure – General Treatment Strategies in Protocol



Ultimate treatment decisions to be made by the Investigator

*Minimum weekly review of PA mean trends

Appendix 2: Hospital admissions at Montreal Heart Institute with a primary diagnosis of heart failure, financial year April 1st 2016 to March 31st 2017

Heart Failure

APRIL 1st 2018 TO MARCH 31st 2019

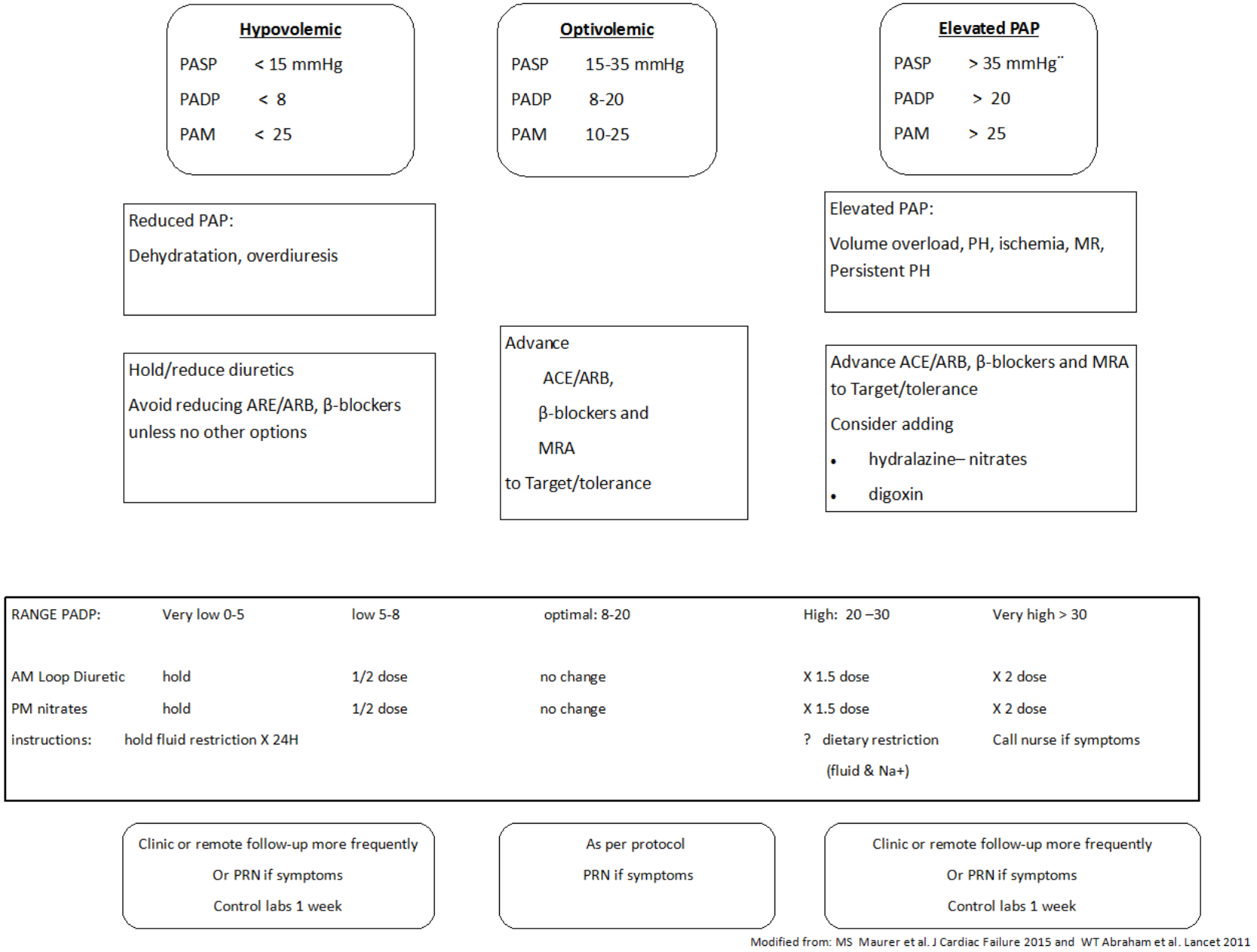
# hospitalizations	# Pts	Mean age	men	women	# emergency department consultations
900	716	76	281	435	1393
			39,20%	60,80%	

Nb Readmission during the same financial year *	
# Readmission	# pts
0	475
1	135
2	65
3	32
4	5
5	2
6	1
7	0
8	0
9	1
	716

* nb of readmission after a first HF episode

Source: Karine Pearson, MHI archives, September 23, 2019

Appendix 3: Example of an individualized therapeutic plan



Modified from: MS Maurer et al. J Cardiac Failure 2015 and WT Abraham et al. Lancet 2011

Appendix 4 World Medical Association Declaration of Helsinki

Clinical Review & Education

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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