PREDICT-CCM Study

ADVANCED HEART FAILURE: THE PREDICTIVE VALUE OF DOBUTAMINE ECHO-STRESS IN THE CLINICAL RESPONSE TO CARDIAC CONTRACTILITY MODULATION THERAPY (CCM)

v.1.2

***Principal Investigator*:** **Dr. Francesco Zanon,**
UO Cardiologia,
Santa Maria della Misericordia H.
ULSS5 Polesana - Rovigo (Italy)

***Promoter*:** **QUOVADIS no-profit Association, Padua (I)**

Q.U.O.V.A.D.I.S. Associazione Riconosciuta "No-Profit"
Galleria Ezzelino, 5 - 35139 Padova (I)
e-mail: info@quovadis-ass.it ; PEC: quovadis-ass@pec.it

Study Coordinator: Dr. Francesco Zanon

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I have read the protocol and accept participating in the study and fulfilling its requirements.

Principal Investigator:
Name _____Francesco_____
Surname ___Zanon_____
Signature _____
Date _____

List of variations v.1.0 → v.1.1

- In the objectives, replace "adequate medical therapy" with "medical and interventional therapy";
- In the inclusion criteria, eliminate “QRS < 130 ms”;
- In the inclusion criteria, correct "F.E." with "E.F."

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ABBREVIATIONS

ADR	Adverse drug reaction
A.E.	Adverse event
ASADE	Anticipated serious adverse device effect
AT	Atrial tachycardia
AV	Atrioventricular
CCM	Cardiac Contractility Modulation
C.E.	European Community
CIP	Clinical investigational plain
CRF	Clinical Report Form
CRT	Cardiac Resynchronization Therapy
CTCAE	Common Terminology Criteria for Adverse Events
DFU	Direction for use
D.D.	Device Deficiencies
EDC	Electronic data collection
ECG	Electro cardio gramma
EHRA	European Heart Rhythm Association
EMA	European Medicine Agency
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (E.U.)
H.F.	Heart Failure
I.B.	Investigator brochure
ICH	International Conference on Harmonisation
IFU	Instruction for use
ITT	Intention-to-treat
LDDSE	Low-Dose Dobutamine Stress Echocardiography
LVESV	Left Ventricular End-Systolic Volume
LV	Left ventricle
LVAT	Left ventricular activation time
LVEF	Left ventricle ejection fraction
NYHA	New York Health Association
OMT	Optimal medical therapy
PM	Pacemaker
PR	Interval between P wave to R wave (ECG measurement)
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
R.V.	Right ventricular
SADE	Serious adverse device effect
SAE	Serious adverse event
SND	Sinus node disease
UO	Unità Operativa
USADE	Unanticipated Serious Adverse Device Effect

Introduction

Heart failure (H.F.) has a very poor prognosis in terms of mortality, quality of life, and functional capacity. It is one of the most important cardiovascular diseases in terms of global prevalence and healthcare costs. Despite appropriate medical care, many patients experience frequent hospitalizations and limitations in daily activities[1].

The prevalence of heart failure ranges between 1% and 3% in the general adult population in industrialized countries. It is expected to increase substantially due to the availability of better diagnostic tools and medical treatments that prolong life after diagnosis of HF[2].

The latest international guidelines on the management of reduced ejection fraction H.F. recommend a timely approach with the simultaneous introduction of the four main categories of drugs (ACE inhibitors or ARNIs, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors). If drug therapy alone is not sufficient or not well tolerated by the subject, or if there is a disorder in the conduction of the electrical impulse (in particular, a left bundle branch block), it is possible to associate it with electrical therapy, which consists of the implantation of biventricular cardiac devices (pacemakers or defibrillators) that resynchronize cardiac contraction (cardiac resynchronization therapy, CRT). These devices work in close synergy with anti-decompensation drugs to curb the progression of heart failure and, in some cases, restore normal cardiac contractility. Cardiac resynchronization therapy, combined with drug therapy, has been shown to improve survival and quality of life by reducing the symptoms of heart failure, increasing exercise capacity, and enabling subjects to resume many of their daily activities.

Cardiac Contractility Modulation (CCM)

CRT is indicated for patients with a large QRS (>130 ms and evidence of left bundle branch block)[3]; however, the percentage of individuals who do not respond to CRT varies between studies, usually between 25% and 33%[4]. Randomized clinical trials have shown that Cardiac Contractility Modulation (CCM) is a treatment option[5] for patients with symptomatic heart failure despite optimized medical therapy and not eligible for CRT. CCM therapy has also been evaluated in patients who have not responded to CRT[6] therapy.

The implanted device for CCM consists of an implantable pulse generator (like a pacemaker) equipped with a transcutaneously rechargeable battery connected to two ventricular leads that transmit high-energy electrical impulses within the absolute refractory period of the myocardial action potential. The device has no pacing or antiarrhythmic functions and is designed to work even in patients already implanted with pacemakers or defibrillators.

The FIX-HF-4[7], FIX-HF-5[8,9], and FIX-HF-5C[10] trials demonstrated the safety and efficacy of the CCM device concerning the following end-points:

- NYHA classroom improvement.
- Improvement in the quality of life (according to the Minnesota Living with Heart Failure Questionnaire – MLHFQ).
- Improvement in functional capacity at the 6-minute walk test (6MWT).

- Increased peak oxygen consumption (VO2).
- Reduction of cardiovascular death and hospitalizations for heart failure.

The CCM has been shown to improve myocardial contractility[11] by improving cardiomyocyte management of intracellular calcium. It exerts short- and long-term effects and positively modulates cardiac cell gene expression.

The Optimizer Smart system has been approved in countries where the C.E. mark applies since October 3, 2016.
The OPTIMIZER Smart System is indicated for use in patients over 18 who have symptomatic heart failure due to systolic left ventricular dysfunction despite medical and interventional therapy. CCM therapy delivered by the OPTIMIZER system has been shown to improve the clinical status, functional capacity, and quality of life and prevent hospital admissions in symptomatic patients with left heart failure who are carefully selected and followed by cardiologists experienced in the treatment of heart failure[12].

The Optimizer Smart device was FDA-approved on March 21, 2019, for delivering Cardiac Contractility Modulation (CCM) therapy. This approval is unique in that it is the first device to be granted "Breakthrough Device" status by the FDA and to have been included in the FDA's review panel for cardiovascular devices – where it received a unanimous recommendation for approval due to its favorable benefit/risk ratio and then obtained PMA approval by the FDA[12].

In the 2021 ESC guidelines for diagnosing and treating acute and chronic heart failure[13], CCM is an "under evaluation" therapy in NYHA class III/IV patients, with LVEF between 25% and 45% and QRS duration <130 ms.

In the consensus paper published in 2024 by the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC)[14], CCM is suggested as a therapy that experienced operators who cooperate in a multidisciplinary team for heart failure should consider if symptoms persist.

It has been evaluated that, for heart failure patients with reduced ejection fraction, the addition of CCM therapy could be more convenient than OMT alone (i.e., the combined use of five classes of drugs that, individually, have already been shown to improve the prognosis of infarcted patients: acetylsalicylic acid, beta-blockers, statins, antagonists of the renin-angiotensin system, and thienopyridines), if we consider a time horizon of the whole life[15, 16].
In selected cases, and when no other therapeutic options are available, CCM can be adjunct in patients who do not respond to CRT[29].
In a recent study[30], CCM significantly improved H.F. in patients with reduced ejection fraction (HFrEF), NYHA class III, and moderately prolonged QRS of 120-149 ms.

Pharmacological stress echocardiography

Pharmacological stress echocardiography is indicated for the diagnosis and treatment of suspected ischemic heart disease or left ventricular dysfunction of suspected ischemic origin. The examination consists of performing an echocardiogram during the infusion of increasing drug doses that stimulate the sympathetic nervous system, stimulating the heart with an effect similar to physical exertion. The heart reacts with increased contraction force and frequency; sometimes, blood pressure can also increase. The examination helps to recognize the possible presence of stress-induced myocardial ischemia.

Other indications of stress echocardiography include quantifying contractile reserve in cardiomyopathies, evaluating cardiac valvulopathy and congenital heart disease, and evaluating diastolic function and pulmonary hypertension. The main advantages of stress echocardiography are its simplicity, low cost, wide availability, and absence of radiation[17, 18].

The most used drugs in this procedure are Dobutamine or dipyridamole.

Dobutamine is a synthetic catecholamine that primarily stimulates β1 adrenergic receptors and, to a lesser extent, α1 and β2 receptors.

The protocol for standard dobutamine examination was defined in the American Society of Echocardiography (ASE) guidelines of 2007[19]. A graduated dobutamine infusion is usually administered at a 5 μg/kg starting dose per minute. The dobutamine infusion aims to achieve a heart rate of 85% of the maximum heart rate predicted for the person's age. The dose of Dobutamine is increased every 3-5 minutes to 10, 20, 30, and finally to 40 μg/kg per minute[20].

On the other hand, the "low-dose" dobutamine stress echocardiography (LDDSE) test is optimal for detecting ischemia and assessing viability by searching for the "biphasic response." A myocardial area increases its contraction at a low dose of inotropic but later becomes hypokinetic or akinetic at higher doses of dobutamine[20].

During the low-dose dobutamine stress echocardiography, the subject is stressed with Dobutamine by standardized incremental infusions of 5, 10, and 20 μg/kg/min. Each infusion dose is administered for a maximum of five minutes[18, 20, 21, 22].

As assessed by low-dose dobutamine stress echo, left ventricular contractile reserve is a helpful marker for predicting functional improvement of the left ventricle and determining long-term prognosis in patients with dilated heart disease[23].

Low-dose dobutamine stress echocardiography has proven to be a simple and effective procedure for selecting patients who are candidates for CRT, having demonstrated the correlation between contractile reserve and response to subsequent resynchronization therapy[24]. The assay was also used to quantify the degree of remodeling after CRT[25] therapy.

Many CRT studies have evaluated left ventricular reverse remodeling by echocardiographic testing with low-dose Dobutamine. A positive response criterion is a reduction of left ventricular end-systolic volume (LVESV) greater than or equal to 15% [26, 27, 28].

Introductory summary

When no other therapeutic options are available, CCM can be a helpful complement to treating heart failure, improving quality of life, and prolonging survival. Still, the high cost and availability of implantations in qualified centers limit its use.

Then, searching for indicators that maximize the benefit/risk ratio is appropriate. According to the study's proponents, the contractile reserve of the left ventricle assessed by stress echo to low-dose Dobutamine may be among the most promising indicators for this purpose.

Objective of the study

The objective of the study is to evaluate the long-term clinical and instrumental response of CCM treatment in adult subjects suffering from symptomatic heart failure due to systolic left ventricular dysfunction despite adequate medical therapy.

End-point assessment will be performed in the entire cohort of enrolled subjects and two sub-cohorts, divided according to the response to stress echocardiography with preimplantation low-dose Dobutamine:

- "DeltaESV>=15%" sub-cohort, with a decrease in LVESV greater than or equal to 15%
- "DeltaESV<15%**"** sub-cohort, with a decrease in LVESV of less than 15%.

Primary End-point

- The proportion of subjects with clinical response to CCM therapy at 12 months (NYHA reduction ≥ 1 class),

Secondary Clinical End-points

1. Reduction in the number of hospitalizations, visits to the Emergency Department, or access to day hospital facilities for more than 4 hours (e.g., by intravenous infusion of cardiac inotropic drugs) compared to the year before the study.
2. Change in the quality-of-life score estimated with the "Quality of Life Questionnaire with Heart Failure – Minnesota" (MLHFQ) between baseline and end of follow-up,
3. Change in walk distance between baseline and end of follow-up in the walk test (6MWT) (optional),
4. Change in NT-proBNP level between baseline and end of follow-up.

Secondary Echocardiographic End-points

1. The proportion of subjects with LVESV decreased by ≥ 15% on echocardiography at end-of-follow-up compared to preimplantation,
2. The proportion of subjects with increased integral velocity time (VTI) ≥ 20% between preimplantation and end-of-follow-up echocardiography,
3. The proportion of subjects with a 20% increase in ejection fraction (LVEF) between preimplantation and end-of-follow-up echocardiography,
4. The proportion of subjects with progression or, conversely, improvement in Mitral Regurgitation (M.R.; classified as mild, moderate, or severe).

Secondary Security End-points

1. The proportion of subjects who, during follow-up, will be evolved to cardiac resynchronization system (CRT) implantation,
2. The proportion of subjects who, during follow-up, will be evolved to left ventricular assist device (LVAD) implantation,

3. The proportion of subjects who will have received a cardiac transplant during follow-up,
4. The proportion of subjects who will die from H.F. during follow-up (it is also compared to the predicted mortality by the "MAGGIC" score[33]).
5. Assessment of the arrhythmic burden (in the case of a patient with an ICD: number of episodes of ventricular tachycardia treated with ATP/shock; in the case of a patient with a Pacemaker/ICD/Loop recorder: percentage of time spent in atrial fibrillation).
6. Rate of all procedure-related adverse events.
7. Potentially harmful factors like the procedure time and fluoroscopy time.
8. Rate of re-operations (lead revision/replacement/infection).

Study population

Inclusion Criteria

- Subject of both sexes with age ≥ 18 years,
- Ability to understand and sign informed consent to participate in the study and consent to process sensitive personal data.
- Carrier of symptomatic heart failure, despite optimal medical therapy (OMT),
- Reduced left ventricular systolic function (E.F. <50%),
- It was positively evaluated for implanting a system for cardiac contractility modulation (CCM) (according to the European Society of Cardiology 2021 Guidelines on heart failure and the provisions of the C.E. mark approval)[13].
- Have presented at least one hospitalization, access to the Emergency Department, or access to day hospital facilities for more than 4 hours (e.g., by intravenous infusion of cardiac inotropic drugs) in the year before implantation.

Exclusion Criteria

- Life expectancy < 1 year due to non-cardiac comorbidities that reduce prognosis,
- Presence of contraindications to the CCM implantation procedure (absence of vascular access usable for CCM implantation, active infectious processes, active severe coagulopathies, presence of mechanical tricuspid valve)[31],
- Contraindications to the performance of the echocardiographic test under pharmacological stress (heart failure in progress, myocardial infarction in the acute phase, acute inflammatory processes of the heart muscle and/or pericardium, critical aortic valve stenosis and severe obstructions to left ventricular outflow, dissecting aneurysm of the aorta, severe arrhythmias not controlled by therapy, known hypersensitivity to the drug, intraventricular thrombi)[21].

Study design

The "Predict-CCM" is an observational cohort, retrospective and prospective, multicenter, independent, non-profit study.

The Promoter is the recognized non-profit association Q.U.O.V.A.D.I.S. of Padua (I).

Dr. Francesco Zanon of UO Cardiologia, S. Maria della Misericordia Hospital, ULSS5 Polesana, Rovigo (I), coordinates the study.

The participating clinical centers are experts in assisting individuals with severe heart failure and implanting cardiac contractility modulation (CCM) systems.

Enrollable subjects who, in the participating Clinical Centers, received a CCM implant from July 1, 2024, to the start of the study will be part of the retrospective cohort, while subsequent subjects of the prospective cohort.
Enrollment in the study will continue for 2 years.
The follow-up period for each subject will be 12 months after implantation.

The study involves clinical-instrumental controls and data collection in eCRF at the time of enrollment, at implantation, at least once between 1 and 6 months of follow-up and twelfth months after CCM implantation.

Medical Device

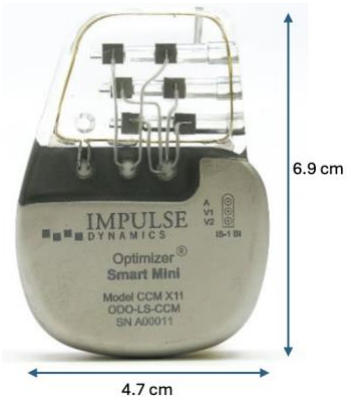
Subjects participating in the study carry or will carry the CE-certified medical device "OPTIMIZER Smart Mini" by Impulse Dynamics (USA). The assignment of a patient involved in the study to CCM through the “OPTIMIZER Smart Mini" system will be determined independently of the patient's participation in the study, and the treatment is part of the routine clinical practice at each involved center. This device delivers Cardiac Contractility Modulation (CCM) therapy. It is indicated for use in patients over 18 years of age with symptomatic heart failure due to systolic left ventricular dysfunction despite appropriate medical treatment.[31]
The OPTIMIZER Smart Mini Implantable Pulse Generator is a programmable device with an internal battery and telemetry functions. The system is suitable for treating heart failure, a condition in which the heart muscle does not pump blood as it should, resulting in reduced cardiac output.
The OPTIMIZER Smart Mini monitors the heart's intrinsic activity. It sends CCM signals to the heart tissue during the ventricular absolute refractory period, when the heart tissue cannot activate, thus making the CCM signal non-excitatory. The CCM signal is sent in sync with the

local electrical activity detected. It can achieve the desired effect on the tissue, i.e., treating heart failure by increasing cardiac output or heart muscle contractility.

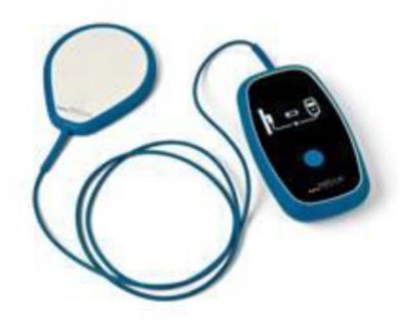
The OPTIMIZER Smart Mini is connected to two or three implantable leads, two of which are implanted in the right ventricle and one, optionally, in the right atrium.

The battery inside the IPG OPTIMIZER Smart Mini is rechargeable via the Vesta[35] charging system.
The Vesta charger is powered by a rechargeable battery and is used by the patient to charge their transcutaneously implanted IPG OPTIMIZER Smart Mini using inductive energy transfer. It incorporates a graphical display that shows a different screen for each operating status, alert, and other information it receives through daily communications with the IPG OPTIMIZER Smart Mini.

The Intelio programmer uses telemetry to query and program the IPG OPTIMIZER Smart Mini. With the Intelio programmer, the clinician can obtain diagnostic data from the IPG OPTIMIZER Smart Mini and customize the operating parameters of the IPG OPTIMIZER Smart Mini to meet the specific needs of each patient[35].



OPTIMIZER Smart Mini



Caricatore Vesta

Programmatore Intelio

Possible complications of device implantation[31]
Like any surgical procedure, implanting an IPG OPTIMIZER Smart Mini has some risks.

Complications of device implantation reported in the literature include, but are not limited to:

- Infection
- Skin necrosis
- Device migration
- Hematoma formation
- Seroma formation

- Histotoxic reactions (see also: Potential adverse effects, Section 7)

Acute and chronic complications reported in the literature include, but are not limited to:

- Lead fracture
- Lead displacement
- Atrial or ventricular perforation
- Rare cases of pericardial tamponade

In sporadic cases (<1%), transvenous lead placement may cause venous thrombosis and subsequent SVC syndrome.

Potential adverse effects[31]

Examples of adverse effects that may occur following the surgical procedure are listed below in order of clinical severity:

1. Death
2. Arrhythmias (brady- or tachyarrhythmias including fibrillation)
3. Stroke or TIA ("transient ischemic attack")
4. Formation of blood clots
5. Respiratory/ventilatory failure
6. AD/VD drilling
7. Hemorrhage
8. Infection
9. Pericardial or pleural effusion
10. Pneumothorax
11. Injury to the heart or blood vessels
12. Heart muscle damage
13. Damage to the tricuspid valve, potentially resulting in regurgitation of the tricuspid valve
14. Damage to the specialized tissue in the heart responsible for initiating each heartbeat (i.e., the heart's conduction system)
15. Pain at the incision site

Examples of additional adverse effects that may occur because of the delivery of MCC therapy are listed below in order of clinical severity:

1. Abnormal heart function
2. Atrial and ventricular tachyarrhythmias
3. Atrial and ventricular bradyarrhythmias
4. Worsening heart failure
5. Damage to myocardial tissue
6. Lead Shift
7. Chest pain

8. Chest wall sensations
9. Inappropriate ICD behavior because of interaction with an implanted IPG OPTIMIZER Smart Mini

Risks associated with Participation in the Clinical Study

All procedures and tests planned for the follow-up period are standard of care. This study is observational, therefore, the risks associated with the implant procedure are to be considered independent of participation in the study..

Additional minimum risks may be linked to the procedure and follow-up testing, which are unforeseen now.

Possible Interactions with Concomitant Medical Treatments

There is no risk of interactions between medical therapies and the study procedures.

Risk Minimization Actions

Additional risks may exist. Risks can be minimized by performing procedures in the appropriate hospital environment, adhering to subject selection criteria, and monitoring the subject's physiological status during research procedures and/or follow-ups.

Anticipated Benefits

The enrolled subject will receive effective and safe treatment for his health problem, potentially improving the disease's symptoms. Furthermore, medical science and future patients may benefit from this study's results.

The Risk to Benefit Rationale

The devices used in the study are CE-marked and have been proven suitable for their intended purpose. There are no unacceptable residual or intolerable risks, and all applicable risks have been addressed by providing appropriate Device Instructions for Use. Evaluating the risks and benefits expected to be associated with using these devices demonstrates that when used under the intended conditions, the benefits associated with their use should outweigh the risks.

Flow chart

Visit / Data to be collected	Enrollment	Procedure (CCM)	between 1 and 6 months of follow-up	12-mo control end-of-study
In-office visit	X		X	X
Informed content	X			
Physical examination	X		X	X
Medical history	X			
Cardiovascular drug therapy	X		X	X
Echocardiographic data	X			X
LDDSE (LVESV)	X			
Procedural data		X		
NYHA score assessment	X		X	X
NT-proBNP	X			X
6MWT *assessment* (optional)	X			X
MLHFQ QoL assessment	X		X	X
Complications (Adverse Events)		X	X	X
Electrocardiographic data (12-lead)	X	X	X	X

Study Procedures

Enrollment visit

Collection of written informed consent
Patients will be given informed consent, which the Ethics Committee approves. Each study procedure will occur after the patient has agreed to participate by signing and dating the informed consent only.
While asking for informed consent, the Investigator will inform the interested party that Participation in the study is voluntary and that refusal will not lead to the loss of any benefit or affect the doctor's relationship. Also, it will be disclosed that withdrawal from the study is possible at any time without providing a specific reason. Before enrolling in the study, each subject will receive a full explanation of the nature and purpose of the study from the Investigator, along with a description of the benefits and risks associated with Participation. A transparent information sheet covering all crucial aspects of the study will be delivered to the subject. Once read, the subject will have the opportunity to ask questions. Sufficient time will be given to consider the various aspects presented before being asked to sign and date the informed consent form. The original copy of the signed and dated Investigator will keep the informed consent form in the study file held in the Center. The subject will receive a copy of the signed and dated informed consent form for future reference.

The consent forms may be signed for retrospective subjects at the first contact following the CCM implantation.

Screening Visit
After obtaining written informed consent, all potentially considered subjects will complete the screening visit.
The visit includes the collection of the following information:

- Demographic data, including age and gender,
- Cardiovascular history,
- Including any cardiac surgery,
- Risk factors, and comorbidity,
- Number of hospitalizations, visits to the Emergency Department, or visits to day hospital facilities for more than 4 hours (e.g., for intravenous infusion of cardiac inotropic drugs),
- Echocardiographic (2D and 3D),
- Electrocardiographic data,
- Low-dose Dobutamine stress echocardiographic examination.

The echocardiographic (2D and 3D) and Low-dose Dobutamine stress echocardiographic examination is the most commonly available imaging technique for evaluating the above factors and the appropriate treatment approach.
A physical examination will also collect body weight, height, and blood pressure data.

The criteria for inclusion and exclusion regarding the subject's eligibility for the study will then be verified.

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent, has been confirmed to meet all inclusion criteria and none of the exclusion criteria, and has had the CCM leads inserted into the subject's vasculature.

Low-dose dobutamine echo-stress
During the low-dose Dobutamine (LDDSE) stress echocardiography procedure, the subject is stressed with Dobutamine by standardized incremental infusions of 5, 10, and 20 µg/kg/min. Each infusion dose is administered for a maximum duration of five minutes.
The LDDSE protocol is considered completed if there is a 10% increase in heart rate.[18, 20, 21, 22]

Blood pressure and ECG are traced at rest, and the end of each LDDSE protocol phase is monitored during the investigation. The infusion is discontinued if any of the following events occur: arrhythmia, angina, hemodynamic decompensation, ECG, or left ventricular wall movement abnormalities in at least two segments.

This study uses two-dimensional echocardiography to evaluate reverse remodeling of the left ventricle during dobutamine echo-stress. The echocardiographic response to the dobutamine stress test is considered positive (presence of contractile reserve) if the reduction in left ventricular end-systolic volume (LVESV) is at least 15% compared to baseline[27].

The parameters to be measured at baseline and each LDDSE protocol phase are as follows:

- End-systolic volume (ml) in biplane,
- End-diastolic volume (ml) in biplane,
- Left ventricular ejection fraction (%) in biplane,
- Degree of mitral regurgitation (mild, moderate, severe),
- Stroke volume (ml) with continuity equation,
- PAPs (mmHg),
- Degree of diastolic dysfunction (first, second, third, fourth degree).

In the case of contraindications to echo-stress with Dobutamine, the subject should not be tested. It cannot be enrolled in the study as reported in the paragraph of "exclusion criteria."

The contraindications to the execution of the echocardiographic test under pharmacological stress are[21]:

- heart failure in progress,
- myocardial infarction in the acute phase,
- acute inflammatory processes of the heart muscle and/or pericardium,
- critical aortic valve stenosis and/or severe obstructions to left ventricular outflow,
- aortic dissecting aneurysm,
- severe arrhythmias not controlled by therapy,
- known hypersensitivity to the drug,
- intraventricular thrombi.

As in current clinical practice, if the subject's home drug therapy involves taking beta-blockers, it must be suspended the day before and on the morning of the LDDSE examination, while if the subject has an implantable cardiac device (pacemaker, defibrillator), it is not indicated to reprogram the pacing mode or the base frequency.

Implanting and programming the Optimizer Smart Mini device

The Optimizer Smart device will be installed according to the instructions given in the user manual.[31]

Two actively fixated leads (conventionally called R.V. and L.S.) are placed in the right ventricle, one preferably in the anterior septum and the other in the posterior septum, about halfway between the base and the apex. An acceptable alternative is to place both leads in an anterior or posterior septal position, provided they are at least 2 cm apart. In patients who have an implantable ICD, ensure that there is adequate separation between the implanted CCM leads and those of the ICD.[31]

In patients who have an implantable ICD, evaluate with a cross-talk test the maximum amount of delay of the CCM series allowed before the ICD begins to perceive CCM therapy impulses as R waves inappropriately.[35]

Technical implant data, including, but not limited to, lead positions, venous access, pacing thresholds, and EGM signals, are reported in the CRF sheets.

Any complications associated with the implant (failure to place the electrode due to inadequate pacing and sensing parameters or repeated electrode dislocation, pericardial effusion, pneumothorax, hemothorax, hematoma of the generator pocket, electrode dislocation) are also collected in the same form.

Optimizer Smart device parameters will be programmed to ensure smooth therapy delivery and maximize therapy percentage according to the directions in the device user manual [31] and programming system.[35]

Under standard conditions, the device is programmed to deliver CCM therapy for seven 1-hour periods distributed equally over the 24 hours of the day.

Follow-up

The first control between 1 and 6 months of follow-up, and the second one at 12 months (± 1 month).

The following data collections are required:

- Physical examination,
- Symptoms, Adverse Events,
- NYHA class variation and Quality-of-life assessment by Minnesota Living with Heart Failure Questionnaire (MLHFQ),
- Cardiovascular drug therapy revision,
- A 12-lead electrocardiogram,
- CCM examination,

Further echocardiographic examinations are required at a 12-month (± 1 month) follow-up visit.

Reintervention for lead revision/replacement
After successful implantation, a Patient needing reintervention for lead revision/replacement will undergo the procedure according to standard clinical practice and the relative information data collected.

Unscheduled visit
An unscheduled visit is an additional visit to those foreseen by the study. The following clinical practice will handle unscheduled visits, and critical clinical data will be collected.

End of Study
The study will end when the last enrolled subject performs the scheduled visit 12 months after enrollment, and the related data will be stored in the CRF.
The Sponsor may terminate this study prematurely, in its entirety, or at any study site, for reasonable and documented reasons, provided that written notice is submitted before the scheduled termination. The Investigator may also stop the study at his site for understandable reasons upon written notification to the Sponsor before the expected end. Either party does not require notice if the study is interrupted due to security reasons. If the Sponsor finishes the trial for security reasons, he must immediately notify the investigators by telephone and provide written instructions for closing the study. The reasons for the Sponsor or Investigator's early termination of a participating site may include but are not limited to the Investigator's failure to proceed following the protocol, with local health authority requirements or with Sponsor procedures, or due to inadequate patient recruitment.

Premature suspension
Enrolled subjects will permanently leave the study when any of the following events occur:

- the occurrence of one of the exclusion criteria,
- a severe adverse event (SAE) that achieves one of the exclusion criteria,
- withdrawal of consent to participate in the study at any time and for any reason,
- if the Investigator deems it necessary in the interest of the patient or if it is no longer compliant with the study procedures (e.g., unavailability for the planned check-ups) or in the case of a female patient who develops a pregnancy,

Prematurely suspended subjects will not be replaced.

Adverse Events

Adverse events, definitions
"Adverse event (A.E.)" is any harmful clinical event that occurs in a subject enrolled in a clinical trial and does not necessarily have a causal relationship with the treatment.

Therefore, an adverse event can be a harmful and unwanted sign (e.g., tachycardia, edema, including an abnormal result of laboratory tests), a symptom (e.g., dyspnea, chest pain), or a disease, regardless of the relationship judgment causal with study treatment. Pre-existing conditions for entering the patient in the study are excluded from the concept of A.E.

"Adverse reaction (ADR)": any A.E. that is believed to be related to study treatment. The definition implies the reasonable possibility of a causal relationship between the adverse event and the study treatment.
The Investigator will assess the causality relationship dichotomously (at least possible relationship/relationship excluded). The ADR definition also includes the study treatment administration's errors, which is different from what the protocol describes.

"Serious adverse event (SAE)": any adverse event (A.E.) that meets one or more of the following criteria:

- It has a fatal outcome
- Immediately endangers the life of the subject
- Requires hospitalization or prolonged ongoing hospitalization *
- It involves a persistent or significant disability or incapacity
- It determines a congenital anomaly or a congenital disability
- It is considered an important medical event in the Investigator's judgment (e.g., an event that requires active intervention to prevent one of the characteristics /consequences mentioned above).

  * *An A.E. is not considered an SAE if hospitalization was scheduled before the subject was enrolled or did not entail the night's stay.*

Serious Adverse Device Effects
A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effects
An unanticipated serious adverse device effect (USADE) is one whose incidence, severity, or outcome has not been identified in the current risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect whose nature, incidence, severity, or outcome has been identified in the risk analysis report.

Device-Specific Events
Device deficiency is the inadequacy of a medical device concerning its identity, quality, durability, reliability, safety, or performance.

NOTE: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer.

Device malfunction means a medical device's failure to perform under its intended purpose when used per the IFU/DFU, I.B., or Clinical Investigational Plan.

Device Deficiencies (D.D.) and other device issues should not be reported as A.E.s. Instead, they should be reported on the appropriate CRF. If an A.E. results from a device deficiency or other device issue, the A.E. should be reported on the appropriate CRF.
Device malfunctions, failures, or deficiencies may or may not cause the subject to experience the harmful effect. By definition, all AE/SAE associated with a device failure is device-related.

Collection, evaluation, and recording of adverse events (A.E.)
At each visit provided by the protocol, the patient will be asked to report any signs or symptoms that arose after the previous visit. The patient will also receive instructions to promptly contact the Center if new signs or symptoms occur between visits. The Investigator must ensure the collection of all the A.E.s occurring in the patient during his stay in the office, not only of the events observed/reported on the occasion of the scheduled views.

The Investigator will evaluate whether a particular medical condition observed in the subject or reported by him can be considered an A.E. based on the interview with the patient, on the physical examination, and, if necessary, on laboratory tests and instrumental examinations of the case.

When the Investigator has identified an A.E., he will register it in the outpatient medical record and the appropriate section of the *Electronic Data Capture (EDC)* platform. In this section, the Investigator will describe the A.E. both freely ("verbatim") and code it according to standard medical terminology (CTCAE v5.0).

Besides, the Investigator for each A.E. will define Severity by the Grading Scale:

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
Grade 2	Moderate	Minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Life-threatening consequences: urgent intervention indicated
Grade 5	Death	Death related to A.E.
Reference: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0		

The period for collecting and recording adverse events (A.E.)
The Investigator will collect and record each A.E. arising from signing the informed consent form until the end of the clinical trial's follow-up period.
The Investigator will follow all the A.E.s registered until their resolution or until, in his opinion, it will no longer be possible to have further information on the event and the outcome.
After the clinical trial closes, the Investigator will communicate to the Promoter any new information about previously registered A.E.s that he should become aware of.

Pre-existing clinical conditions
The clinical conditions present when the informed consent form is signed will be registered as "pre-existing" in the appropriate section of the EDC platform.
Any new clinical condition or worsening of a pre-existing clinical condition that arises after signing the informed consent form will be recorded as A.E., except for the clinical events identified in this protocol as an end-point.

Abnormal laboratory values
Abnormalities of laboratory values that require clinical intervention (e.g., therapeutic measures), further investigations (other than simple repetition of the test), or that are considered clinically significant by the Investigator will be recorded as A.E.

Pregnancies
Should pregnancy occur, the patient will early terminate her Participation in the trial. Pregnancy per se is not considered an A.E. unless there is a suspicion that experimental treatment has interfered with contraceptive systems' effectiveness.
In any case, the pregnancy must be registered and followed until its conclusion.

Efficacy end-point
Clinical events identified in this protocol as an efficacy end-point will not be recorded as A.E.
Reporting of adverse events

Serious adverse events (SAE) and serious adverse device effect (*SADE)*
The Investigator is required to register each SAE and SADE on the EDC platform within three calendar days of its knowledge.
The EDC platform automatically sends an alert email to the Study Coordinator for each registered SAE and SADE.
If there is a lack of information on the SAE and SADE, the Study Coordinator will contact the Investigator to obtain an update.
If the SAE and SADE are fatal or have endangered the patient's life, the Study Coordinator will contact the Investigator to obtain a detailed clinical report on the event.

Non-serious adverse events

The Investigator must also record all non-serious adverse events during the clinical trial (including the follow-up period) in the appropriate section of the EDC.

Pregnancies

Any pregnancy cases and new information on pregnancies reported must be registered and transmitted to the Study Coordinator within 48 hours of learning them.

Relationship to the device or procedure

The Investigator will use the following definitions to assess the relationship to the device or procedure:

Not Related: Relationship to the device or procedure can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the device or the procedure;
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the event;
- the event involves a body site or an organ not expected to be affected by the device or procedure; the event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment, or other risk factors);
- the event does not depend on a false result given by the device used for diagnosis, when applicable; harms to the subject are not clear due to use error;
- To establish the non-relatedness, not all the criteria listed above might be met simultaneously, depending on the type of device/procedures and the event.

Unlikely Related: The relationship with the use of the device or procedure seems irrelevant, and/or another cause can reasonably explain the event, but additional information may be obtained.

Possibly Related: The relationship with using the device or procedure is weak but cannot be completely ruled out. Alternative causes are also possible (e.g., an underlying or concurrent illness or clinical condition or an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed or no information is obtained should also be classified as possibly related.

Probably Related: The relationship with the device or procedure's use seems relevant, and/or another cause cannot reasonably explain the event, but additional information may be obtained.

Causal Relationship: The event is associated with the device or with procedure beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of

similar devices and procedures;
- the event has a temporal relationship with device use/application or procedure;
- the event involves a body site or organ that a device or procedure is applied to and/or affects;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the device used for diagnosis, when applicable;
- Only some of the criteria mentioned above might be met simultaneously to establish their relatedness.

If the relationship between any adverse event and the device's use is considered unlikely, possibly, or probably related, that event will be classified as an ADE or SADE.

Safety Reporting

Safety surveillance within this study and safety reporting performed by the Investigator and Sponsor starts as soon as the subject is enrolled. Safety surveillance and reporting will continue until the last investigational visit has been performed, the subject is deceased, concludes their Participation in the clinical investigation, or the subject withdraws from the clinical investigation. All adverse event data, including deaths, will be collected throughout the abovementioned period and reported to the Study Sponsor through the EDC platform. Additional information on an adverse event should be updated within the appropriate case report form. Unchanged, chronic, non-worsening, or pre-existing conditions are not A.E.s and should not be reported.

For this clinical study, the following events will be reported:

- Serious adverse events
- Adverse events that are considered related to either the leads or the MCC implantation procedure by the Investigator

Non-cardiac-related abnormal laboratory values will not be regarded as A.E.s unless:

- The Investigator determined that the value is clinically significant,
- The abnormal lab value required intervention, or
- The abnormal lab value required the subject to terminate the study.

The Investigator will further report the SAE to the local E.C. according to the institution's E.C. reporting requirements.

Data Collection

Source Data
All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are in source documents (original records or certified copies). Any data recorded directly on the CRFs (i.e., no prior written or electronic record of data) is considered source data.

Source Documents
Original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, or records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial).
All parameters asked for in the case report form (CRF) should be documented in the source documents.

Document retention
The Study sponsor and the Principal Investigators will maintain the clinical investigation documents as required. Measures will be taken to prevent accidental or premature destruction of these documents.
These documents must be retained for 10 years after the clinical investigation concludes and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.
All source documents must be stored for the maximum time required by the hospital's regulations, research institute, or practice.

Electronic Data Collection
An "Electronic Data Capture" (EDC) system based on the "Research Electronic Data Capture" platform (REDCap, produced and distributed by Vanderbilt University and "REDCap Consortium") will be used for the collection of data in the various participating Centers.
The eCRF (clinical data collection forms) can be consulted as an accompanying document to the protocol.

Data protection
The personal data of the enrolled subjects will be treated with the utmost confidentiality under the provisions of Italian Legislative Decree 211/2003, subsequent amendments and additions, and E.U. Regulation 2016/679 ("GDPR"). In particular, the subject's personal data

will be known only to the Investigator and his collaborators who follow the patient and collect their consent for the treatment. A unique numerical identification number will be used to identify each enrolled subject.

An administrator guarantees the use and maintenance of the REDCap platform by managing users with a flexible and granular authorization system. REDCap applies the permissions granted to each user who connects to it through a web browser and the protocol with SSL encryption (using a personal "username" and "password"), activating certain functions, tabs, links, and buttons according to the privileges granted and the group/center of belonging.
REDCap allows a complete "audit" of user procedures, recording all data operations, including viewing and exporting. The operational control log stores the date, time, and user who operates, allowing a complete review and remote monitoring of the clinical study if necessary.
All users who have access to the EDC platform, investigators, staff members, and data managers must have attended a training event to increase the reliability, quality, and integrity of the data recorded on the platform.

REDCap implementations allow compliance with the most common industry standards and EMA requirements (GCP, Privacy-IT: DL 211/2003 and subsequent amendments and additions; E.U. Regulation 2016/679 "GDPR") and FDA (21-CFR2-Part 11).

Every effort is made to ensure compliance with the "GCDMP" guidelines (Good Clinical Data Management Practice, published by the Society for Clinical Data Management, 2013), in particular for the reliability, quality, integrity, and security of data registered on the EDC platform, both from a procedural and I.T. point of view with the use of "state of the art" solutions.

STATISTICAL ANALYSIS

General Statistical Methods
All variables will be analyzed descriptively with the appropriate statistical methods: for categorical variables using frequency tables and continuous variables with sample statistics (e.g., average, median, standard deviation, minimum and maximum value, 25 ° and 75 ° quartile).
The selected baseline covariates may be compared for 'like-to-like' in the two sub-cohorts of subjects with appropriate statistical tests for discrete and continuous variables.
Unless otherwise specified, all statistical tests will be 2-tailed and at a significance level of 5%.
All primary and secondary analyses will be performed on the modified intention-to-treat (ITT) population, which includes all enrolled subjects who have undergone CCM implantation.
Subjects who will be enrolled but withdraw consent before undergoing the CCM implant procedure can be replaced, even if they do not lose their unique identification code.

Subjects who leave the observation without presenting the end-point will be considered censored and considered to have participated in the risk during the observation period.
For those not present for the clinical evaluations at the control between the 1st to 6th month and 12th month of observation, every effort will be made to determine a possible outcome of interest for the study and make them assessable as end-points.

The overall sample size is justified by hypothesis parameters and driven by the primary end-point to preserve its adequate statistical power.
The primary end-point: Proportion of subjects with clinical response to CCM therapy at 12 months (NYHA reduction ≥ 1 class).

Hypotheses

Based on the analysis of the on-topic (poor) scientific literature and our experience in the field, we can hypothesize that:

1. In all subjects, the proportion of subjects with clinical response to CCM therapy at 12 months (NYHA reduction ≥ 1 class) of follow-up will be near 70%,
2. The proportion of subjects who will have a positive response to LDDSE before CCM implantation (i.e., with a decrease in LVESV greater than or equal to 15%) will be 80%.

Sample size estimation

When the proportion of subjects with clinical response to CCM therapy at 12 months is 70%, a sample size of 120 will produce an acceptable two-sided 95% confidence interval with a width equal to 17%.
As Figure 1 shows, this sample size will allow us to be adequately confident even in modest variations in the expected proportion.

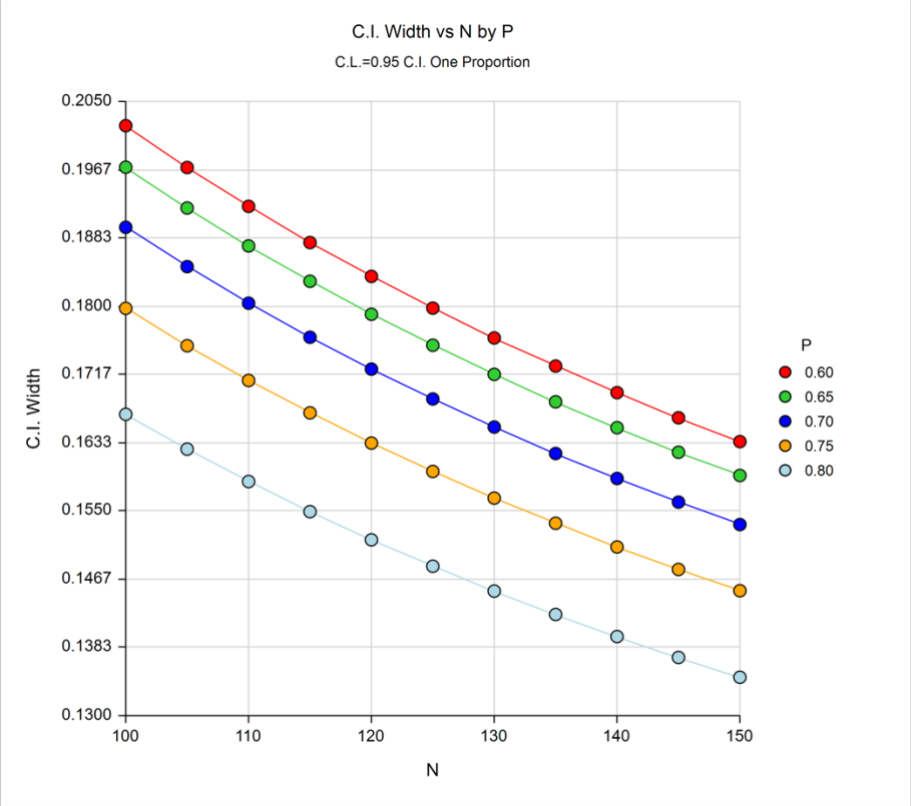


Figure 1

Legend:
P: clinical response proportion in the comprehensive cohort,
N: sample size
C.I. Width: width of 95% Confidence Limits

Under Hypotheses 2, the two sub-cohorts will be composed of:
80 subjects in the "**DeltaESV>=15%**", where we assume a clinical response to CCM therapy at 12 months around 80%, and
40 subjects in the "**DeltaESV<15%**", where we assume a clinical response to CCM therapy at 12 months around 40%,

We should have adequate power to evaluate the prognostic contribution of a positive LDDSE test, even in the presence of minor variations in the observed responses compared to the expected ones (Figure 2).

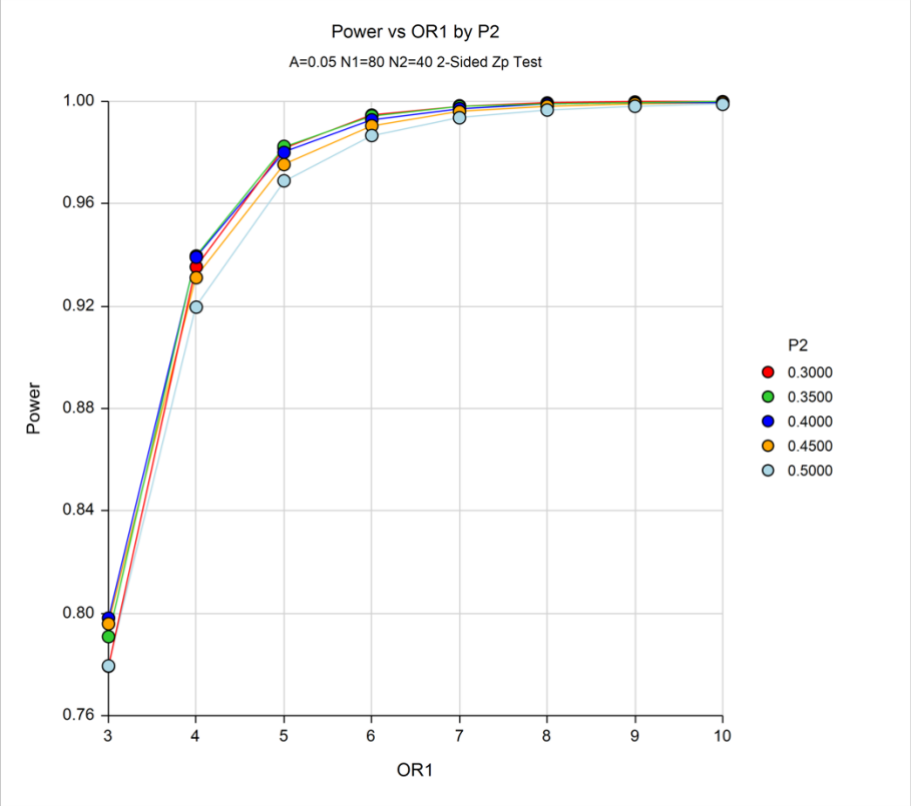


Figure 2

Legend:
P2: clinical response proportion in sub-cohort "DeltaESV<15%",
OR1: Odds Ratio ("DeltaESV>=15%" versus "DeltaESV<15%")

The power was estimated by PASS v.11 (NCSS Inc., Kaysville, Utah, USA).

Statistical analysis specifications
The purpose of the study is predominantly descriptive.

Primary End-point
The proportion of subjects with clinical response to CCM therapy at 12 months (NYHA reduction ≥ 1 class) will be estimated with its 95% C.L. for the entire cohort and the two sub-cohorts. In this case, the crude O.R. for clinical response between the sub-cohorts ("DeltaESV>=15%" versus "DeltaESV<15%") will be estimated with his 95% C.L., and the Fisher Exact test will evaluate the association between the two factors.

A multivariable logistic regression will test the likely presence of risk factors for the primary efficacy end-points and provide the correct O.R. estimation for any other clinical or instrumental descriptors that characterize the enrolled subjects. Those descriptors significantly associated ($p<0.10$) with the clinical response in the univariate analysis will be introduced into the multivariable regression and further selected using the Forward Stepwise Wald method.

Secondary End-points

All continuous secondary end-points will be summarized with the number of non-missing data, mean ± standard deviation, median, and range (minimum-maximum). All categorical secondary end-points will be tabulated with the occurrence and proportion with its 95% CI. A paired t-test will be used for the comparison within the group, and the equivalent non-parametric test, such as the signed-rank test or sign test, will be used if the assumption for the paired t-test is violated. Comparison between groups will be performed using a t-test or equivalent non-parametric tests, such as the Wilcoxon rank-sum test or Kolmogorov-Smirnov test, when the assumption for the t-test is violated.

All categorical secondary end-points will be tabulated by occurrence and percentage. Then, Fisher's exact test will be used to compare the groups.

All statistical analyses will be performed using SPSS Statistics, version 26 or later (IBM Corp. Armonk, NY), and STATISTICA v12 (StatSoft, Tulsa, OK).

Final report and publication of the results

The study results will be reported in a final integrated, statistical, and clinical report compliant with the GCP-ICH-E6, STROBE, and TRIPOD guidelines. The report's content will be approved jointly by the Clinical Coordinator of the study and the Promoter.

The same joint approval will apply to the contents of the first publication and the first public presentation of the study results, which the Promoter undertakes to carry out even if there is negative evidence of them. Any secondary publications or presentations will be subject to prior notification by the Coordinator to the Promoter or vice versa, with the recipient's capacity to comment.

ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial will follow the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by the World Medical Assemblies (the latest revisions of the WHO Declaration of Helsinki, 2024), the Declaration of Oviedo, and the ICH guidelines for Good Clinical Practice (ICH-E6-R2).

This clinical trial will comply with all international laws and regulations, the national laws and regulations of the country where it is performed, and any other applicable guidelines.

Responsibilities of the Investigator(s)

The Investigator (s) undertake(s) the responsibility to perform the study following this Protocol, Good Clinical Practice, and the applicable regulatory requirements. The Investigator must ensure compliance with the investigational product schedule, visits schedule, and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form (CRF) accurately and legibly. The Investigator

may implement a deviation from or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior E.C. approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted. The Investigator must have an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

Participant subjects

Each subject may be enrolled after reviewing the relevant information and signing the informed consent forms for participation in the study and consent to process sensitive personal data.

For retrospective subjects, the consent forms may be signed at the first contact following the installation of the CCM.

Ethics Committee (E.C.) Approvals

This clinical trial protocol, as well as the informed consent, are to be submitted to the appropriate Ethics Committee, and it is mandatory to obtain the written and dated approval, signed by the chairman with Ethics Committee(s) composition.

The clinical trial, the documents reviewed, the list of voting members and their qualifications, and the review date should be clearly stated on the written Ethics Committee approval.

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