Retirada del tratamiento neurohormonal en pacientes con miocardiopatía no isquémica, sin realce tardío de gadolinio y con test genético negativo, que hayan sido super-respondedores a la terapia de resincronización cardiaca.

Ensayo clínico DRUGLESS-CRT.

SYNOPSIS OF THE STUDY

Title	Withdrawal of heart failure treatment in patients with non-ischemic cardiomyopathy, without late gadolinium enhancement and with a negative genetic test, who have been super-responders to cardiac resynchronization therapy.
Code	DRUGLESS-CRT
Sponsor	Dr. Andrea Di Marco
Research team	Dr. Laia Lorenzo, Dr. Jesus Sanchez Vega, Dr. Raul Ramos, Dr. Cristina Enjuanes, Dr. Fernando De Frutos, Dr. Carles Diez Lopez, Dr. Jose Gonzales Costello, Dr. Lorena Herrador Galindo, Javier Sanau Martin, Dr. Eduard Claver, Dr. Jaume Francisco Pascual, Dr. Jose F. Rodriguez Palomares, Dr. Toni Soriano Colomé, Dr. Jose Guerra Ramos, Dr. Marta de Antonio Ferrer, Dr. David Viladés Medel, Laura Triguero Llonch, Dr. Juan Jimenez Jaimez, Laura Jordan, Dr. Rosa Macías, Dr. Carles Moliner Abos, Dr. Aleix Fort, Dr. Paloma Jordá, Dr. Inés Ponz, Dr. Esther Perez David, Dr. Ignasi Anguera, Dr. Josep Comín-Colet.
Event evaluation committee	Jesus Sanchez Vega, Lorena Herrador Galindo, Raul Ramos, Javier Sanau, Julián Rodriguez García
Study design	Multicenter (6 Spanish hospitals), prospective, non-inferiority, randomized, single-blind (primary endpoint evaluators blinded, patients not blinded).
Hypothesis	The withdrawal of heart failure treatment is safe in patients with non-ischemic cardiomyopathy, negative genetic test, no evidence of late gadolinium enhancement on cardiac MRI, who have been super-responders to cardiac resynchronization therapy and remain free of heart failure events for at least 6 months after device implantation.
Primary endpoint	Recurrence of left ventricular dysfunction or heart failure symptoms at 6 months (any of the following events): - Decrease in LVEF >10% and final LVEF <50% - Decrease in LVEF >10% and increase in LV end-systolic volume >15%

	- Appearance of heart failure symptoms accompanied by elevated NT-proBNP requiring initiation of oral, subcutaneous, or intravenous loop diuretic treatment.
Secondary endpoints	- Emergency room or day hospital visits for heart failure - Hospitalizations due to heart failure - Ventricular arrhythmias - Supraventricular arrhythmias - NT-proBNP levels - NYHA functional class - Quality of life
Follow-up	The primary and secondary endpoints will be analyzed initially at 6 months from study inclusion. If the drug withdrawal strategy proves safe during this period, follow-up will continue up to 12 months with a new evaluation of all endpoints.
Study duration	- Inclusion: 6 months - Follow-up until primary endpoint: 6 months - Total follow-up until end of study: 12 months
Inclusion criteria	- Diagnosis of non-ischemic cardiomyopathy - LBBB already present at the time of first diagnosis of LV dysfunction - Negative genetic test - Cardiac MRI with no evidence of late gadolinium enhancement (LGE at RV insertion points is acceptable) - Carrier of a resynchronization device (ICD or pacemaker, with LV epicardial pacing form a cardiac vein or left bundle area pacing), pacing percentage >95% and paced QRS <140 ms - Device indication: LVEF ≤35% and LBBB with QRS >150 ms - LVEF ≥50% and normal indexed LV volumes on echocardiogram performed at least 6 months after CRT implantation - No heart failure decompensations (no hospitalizations or urgent/day hospital visits) since CRT implantation - No need for loop diuretic treatment - NYHA class I or II - NT-proBNP <450 ng/L (or <1000 ng/L in atrial fibrillation/flutter) - On neurohormonal therapy with at least two drugs
Exclusion criteria	- Family history of non-ischemic cardiomyopathy with LVEF <50% in at least one first-degree relative - Severe valvular heart disease - History of sustained ventricular arrhythmia or treated by ICD - Need to maintain beta-blocker therapy for other

	arrhythmias - Hypertension not controlled with other medications - CRT devices implanted as an upgrade from prior pacemaker or ICD, where prior pacing percentage was >20% - Clinical indication other than heart failure to maintain any of the neurohormonal treatment drugs (class I recommendation in ESC or ACC/AHA guidelines)
Sample size	64 patients, 32 in each treatment group
Study procedures	- Neurohormonal treatment withdrawal: will be performed progressively over a maximum of 9 weeks, discontinuing drugs one by one following a predefined sequence - Echocardiogram (centralized analysis) at baseline, 6 and 12 months - In-person clinical and lab evaluation 2 weeks after completing drug withdrawal (intervention group) or at 10 weeks post-inclusion (control group), and at 6, 9, and 12 months after randomization - Weekly phone visits during withdrawal phase (intervention group), or at weeks 4 and 8 (control group), and at weeks 16 and 20 - In-person CRT interrogation at 6 and 12 months

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with left bundle branch block (LBBB) and severe left ventricular dysfunction despite optimal medical therapy.[1] In some cases, CRT can normalize left ventricular function, achieving a left ventricular ejection fraction (LVEF) >50%. These patients are defined as **super-responders to CRT**.

The prevalence of super-responders is higher in non-ischemic cardiomyopathy (NICM) than in ischemic heart disease.[2] In a multicenter cohort of patients with NICM undergoing CRT, we observed that 33% were super-responders.[3]

The prognosis of super-responders is generally excellent, with an almost negligible risk of both ventricular arrhythmias and severe heart failure-related events.[2]

In patients with NICM, the absence of localized myocardial fibrosis—assessed by late gadolinium enhancement (LGE) on cardiac magnetic resonance—has been associated with a better prognosis. Patients without LGE have a lower risk of heart failure hospitalizations, a very low risk of ventricular arrhythmias, and reduced mortality.[4-5]

Genetics is another factor with an independent prognostic impact in NICM. Patients with a positive genetic test (pathogenic or likely pathogenic variants) have a higher risk of both heart failure events and severe ventricular arrhythmias.[6]

Both LGE and genetic background also influence prognosis in patients with NICM treated with CRT. In this population, the absence of LGE is associated with a higher likelihood of response and super-response to CRT, as well as an almost negligible risk of sustained ventricular arrhythmias or sudden cardiac death.[3,7] More recently, a negative genetic test has also been associated with a higher probability of response or super-response to CRT and with a lower risk of death due to heart failure, heart transplantation, or need for left ventricular assist device implantation.[8]

Therefore, patients with NICM, no LGE, a negative genetic test, and who are super-responders to CRT combine several features associated with excellent prognosis. These patients could be considered the prototype of a **"dyssynchronopathy"**, that is, a form of left ventricular dysfunction essentially secondary to an abnormal intra- and interventricular electrical conduction. Consequently, CRT may represent the main—and possibly the only—truly necessary treatment in these patients.

It should be noted that all these patients had previously received optimal heart failure therapy (neurohormonal treatment) before CRT implantation, and this therapy had failed to reverse severe left ventricular dysfunction. Despite this, neurohormonal therapy at the maximum tolerated dose is maintained indefinitely, as no studies have evaluated the safety of complete withdrawal of neurohormonal therapy in NICM patients who are super-responders to CRT.

The STOP-CRT clinical trial included 80 patients with non-ischemic cardiomyopathy who were super-responders to CRT and randomized them into four groups:

1. continuation of all neurohormonal therapy,
2. withdrawal of beta-blocker only,
3. withdrawal of ACE inhibitor/ARB only,
4. withdrawal of both beta-blocker and ACE inhibitor/ARB.

After two years of follow-up, the cumulative incidence of the primary endpoint (increase in LV end-systolic volume >15%) was relatively low (7%) in the withdrawal groups, with no significant differences compared to the control group.[9] Moreover, no hospitalizations due to heart failure or cardiovascular deaths occurred in the experimental groups. However, in that trial, most patients continued mineralocorticoid receptor antagonists (MRA), and neprilysin inhibitors (ARNI) and SGLT2 inhibitors were not included, as they were not yet widely available.

Interestingly, the recent WITHDRAW-AF trial demonstrated the safety of withdrawing all neurohormonal therapy (including MRA, ARNI, and SGLT2 inhibitors) in 60 patients without LGE diagnosed with tachycardiomyopathy.[10] These patients had developed left ventricular dysfunction in the context of supraventricular arrhythmia and recovered LVEF after restoration of sinus rhythm. In this study, there were no significant differences in LVEF at 6 months between patients who discontinued therapy and those who continued treatment. Furthermore, none of the patients in the withdrawal group developed heart failure symptoms or required hospitalization for decompensated heart failure.

This trial suggests the potential safety of withdrawing neurohormonal therapy in patients who have recovered normal LVEF after correction of the main underlying cause of ventricular dysfunction. In WITHDRAW-AF, this cause was arrhythmia; in the present study, it is electrical dyssynchrony. In addition, WITHDRAW-AF also used absence of LGE as an inclusion criterion to exclude patients with underlying structural cardiomyopathy. In our study, we aim to be even more selective by including only patients without LGE and with a negative genetic test.

It is important to note that neurohormonal therapy may be associated with adverse effects, including symptomatic hypotension (dizziness, fatigue), electrolyte disturbances, and renal dysfunction. Furthermore, these treatments are costly and should only be maintained lifelong if a clear benefit is demonstrated. Finally, current neurohormonal therapy consists of multiple drugs, and polypharmacy is a well-recognized cause of poor adherence. Therefore, reducing the number of medications may also improve adherence to other essential treatments.

In light of all the above, we believe it is both appropriate and necessary to assess whether it is safe to discontinue neurohormonal therapy in patients with NICM, no LGE, negative genetic testing, who are super-responders to CRT and remain clinically stable without heart failure events after device implantation.

HYPOTHESIS

Withdrawal of neurohormonal therapy is safe and non-inferior to its continuation in patients with non-ischemic cardiomyopathy, without late gadolinium enhancement, with a negative genetic test, who have been super-responders to cardiac resynchronization therapy.

OBJECTIVES

Primary objective

To demonstrate that withdrawal of neurohormonal therapy is non-inferior to its continuation with respect to recurrence of left ventricular dysfunction or heart failure symptoms in patients with non-ischemic cardiomyopathy, without late gadolinium enhancement, with a negative genetic test, who have been super-responders to cardiac resynchronization therapy.

Secondary objectives

To demonstrate that withdrawal of neurohormonal therapy is non-inferior to its continuation with respect to:

Hospitalizations due to heart failure

Occurrence of ventricular or supraventricular arrhythmias

NT-proBNP levels

NYHA functional class

Quality of life

METHODS

Study design

Multicenter, prospective, randomized, non-inferiority, single-blind study: the cardiologists performing follow-up echocardiograms, as well as the event adjudication committee responsible for evaluating primary and secondary endpoints, will be blinded to treatment allocation. Patients, however, will not be blinded.

Subjects meeting all inclusion criteria, none of the exclusion criteria, and who provide informed consent will be randomized to the intervention or control group in a 1:1 ratio.

To ensure balance between groups, the randomization list will be generated using blocks of random size (4, 6, and 8 subjects) and will be stratified by:

- Sex
- Age categories (<60 years, 60–75 years, >75 years)
- LVEF categories (50–55% and >55%)

The randomization process will be centralized and implemented within the electronic data capture system.

Inclusion criteria

- Age >18 years
- Diagnosis of non-ischemic cardiomyopathy
- Negative genetic test (at least 50 genes analyzed)
- Cardiac magnetic resonance imaging without evidence of late gadolinium enhancement (LGE at right ventricular insertion points is acceptable)
- Carrier of a cardiac resynchronization device (ICD or pacemaker), with either:
    - Left ventricular epicardial pacing via a coronary vein, or
    - Left bundle branch area pacing

  with:

    - Pacing percentage >95%
    - Paced QRS duration <140 ms
- Initial indication for CRT:
    - LVEF ≤35% and
    - LBBB with QRS >150 ms
- LVEF ≥50% and normal indexed LV volumes on echocardiography performed at least 6 months after CRT implantation
- No heart failure decompensation (no hospitalizations, emergency department visits, or day hospital visits) since CRT implantation
- No requirement for loop diuretic therapy
- NYHA functional class I or II
- NT-proBNP <450 ng/L (or <1000 ng/L in atrial fibrillation/flutter)
- On neurohormonal therapy with at least two drugs

Exclusion criteria

- Severe valvular heart disease
- History of sustained ventricular arrhythmia or arrhythmia treated by ICD
- Need to maintain beta-blocker therapy for other arrhythmias
- Hypertension not adequately controlled with alternative medications
- CRT devices implanted as an upgrade from a previous pacemaker or ICD when prior pacing percentage was >20%

Primary endpoint

Recurrence of left ventricular dysfunction or heart failure at 6 months, defined as any of the following:

- Decrease in LVEF >10% with a final LVEF <50%
- Decrease in LVEF >10% and increase in left ventricular end-systolic volume >15%
- Development of heart failure symptoms accompanied by an increase in NT-proBNP requiring initiation of:
    - Oral loop diuretics
    - Subcutaneous diuretics

  - Intravenous diuretics

A clinically relevant NT-proBNP increase will be defined as:

- A value >2 times the level recorded during the screening period
- AND above age-adjusted normal values

Secondary endpoints

- Emergency department or day hospital visits due to heart failure at 6 and 12 months
- Hospitalizations due to heart failure at 6 and 12 months
- Ventricular arrhythmias at 6 and 12 months
- Supraventricular arrhythmias at 6 and 12 months
- NT-proBNP levels at 6 and 12 months
- NYHA functional class at 6 and 12 months
- Quality of life at 6 and 12 months
- Recurrence of left ventricular dysfunction or heart failure (as defined for the primary endpoint) at 12 months

Sample size

Considering:

- Alpha error: 2.5%
- Power: 80%
- Expected cumulative incidence of the primary endpoint:
  - 0% in the control group
  - 3% in the experimental group
- Non-inferiority margin: 6%
- Loss to follow-up: 10%

A total of **64 patients** will be required (32 per group).

Statistical analysis

Statistical analysis will be performed using **STATA Release 12 (StataCorp LP)** and **R version 4.2.2**.

- Continuous variables will be described using:
  - Mean and standard deviation, or
  - Median and interquartile range, depending on distribution
- Categorical variables will be described as:
  - Number of non-missing observations
  - Percentages by column

Primary endpoint

- Analyzed using the **chi-square test for paired data**
- Relative risk (RR) and corresponding confidence intervals will be reported

Secondary endpoints

- Continuous variables:
  - Paired Student's t-test
  - Wilcoxon signed-rank test (if non-normal distribution)
  - Effect sizes and 95% confidence intervals
- Categorical variables:
  - Chi-square test for paired data
  - Relative risk (RR) with 95% confidence interval
- Heart failure events:
  - Cox regression analysis

All analyses will be conducted according to the **intention-to-treat principle**.

STUDY PROCEDURES

Genetic test evaluation

Centralized evaluation of genetic tests by at least one cardiologist specialized in cardiovascular genetics to confirm eligibility.

Withdrawal of neurohormonal therapy

Therapy will be withdrawn progressively under strict clinical monitoring.

- One drug will be reduced or discontinued per week following this sequence:
  1. SGLT2 inhibitors
  2. Mineralocorticoid receptor antagonists (MRA)
  3. ACE inhibitors / ARNI
  4. Beta-blockers
- SGLT2 inhibitors will be directly discontinued
- For beta-blockers, ACE inhibitors, and ARNI:
  - If dose ≤25% of maximum → discontinue
  - If higher → reduce by 50% weekly until ≤25%, then discontinue
- For MRA:
  - If dose ≤50 mg → discontinue
  - If higher → progressive weekly reduction

The full withdrawal process is expected to take **up to 9 weeks**.

Echocardiography

- Performed according to a standardized protocol
- Centralized analysis at Hospital de Bellvitge
- Evaluators blinded to treatment allocation

Quality of life assessment

- EUROQOL 5D-5L questionnaire

Endpoint adjudication

- Conducted by an independent committee
- At least two reviewers per case
- Third reviewer in case of disagreement
- All evaluators blinded to treatment group

PATIENT MANAGEMENT DURING THE DIFFERENT STUDY PHASES

Screening period (maximum 30 days)

Patients considered potential candidates for the study will undergo evaluation during a screening period to confirm that they meet all inclusion criteria and none of the exclusion criteria.

Prior to the start of the screening phase, patients must sign the informed consent form.

The screening period will last a maximum of 30 days, during which the following assessments will be performed:

- Transthoracic echocardiogram according to the study protocol
- Baseline laboratory tests including:
    - Complete blood count
    - Ferritin
    - Transferrin saturation
    - Creatinine
    - Urea
    - Estimated glomerular filtration rate

    - Sodium (Na)
    - Potassium (K)
    - NT-proBNP
    - Troponin
    - Creatine kinase (CK)
    - CK-MB
- Electrocardiogram (ECG)
- CRT device interrogation to assess:
    - Ventricular pacing percentage
    - Absence of sustained ventricular arrhythmias or ICD therapies
- Clinical assessment of NYHA functional class

Inclusion and randomization visit

(Performed after confirmation of eligibility criteria)

Neurohormonal therapy withdrawal period (maximum 9 weeks)

During this phase, patients in the intervention group will undergo withdrawal of all neurohormonal therapy according to the predefined protocol.

Patients will be monitored through **weekly telephone follow-up**, which may be conducted by specialized heart failure nursing staff.

During these calls, the following will be assessed:

- Heart failure symptoms
- Body weight
- Heart rate
- Blood pressure

These parameters will be used to determine whether the patient is suitable to proceed to the next step of treatment withdrawal.

If any telephone follow-up suggests the onset of heart failure symptoms:

- The patient will be scheduled for an in-person clinical evaluation
- Laboratory testing will be performed
- Further withdrawal will be temporarily halted until heart failure is ruled out or confirmed

During this period, patients in the control group will receive telephone follow-up at:

- Week 4
- Week 8

At each telephone contact, current medication will be recorded.

Follow-up after completion of neurohormonal therapy withdrawal

A face-to-face clinical visit and laboratory testing (identical to screening) will be performed:

- 2 weeks after completion of withdrawal (intervention group), or
- 10 weeks after randomization (control group)

Subsequently, both groups will be evaluated at:

- 6 months
- 9 months
- 12 months

Telephone follow-up visits will be conducted at:

- Weeks 16 and 20 after randomization

At **6 and 12 months**, the following will be performed:

- Transthoracic echocardiogram
- ECG
- CRT device interrogation
- Quality of life assessment

Patients in the intervention group reaching the primary endpoint

If a patient in the intervention group reaches the primary endpoint:

- A complete in-person clinical evaluation will be performed
- If clinically appropriate, neurohormonal therapy will be **reinitiated immediately**, with progressive titration similar to that used in patients starting therapy for the first time

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RELEVANT DEFINITIONS FOR THE STUDY

Non-ischemic cardiomyopathy (NICM)

Defined as prior occurrence of left ventricular dysfunction in the absence of:

- Significant coronary artery disease:
  - 70% stenosis in major coronary arteries or
  - 50% in left main
- Severe organic valvular disease
- Other cardiomyopathies:
  - Hypertrophic cardiomyopathy
  - Arrhythmogenic right ventricular cardiomyopathy
  - Cardiac amyloidosis
  - Cardiac sarcoidosis

Negative genetic test

Defined as a genetic test for cardiomyopathy that does not identify:

- Pathogenic variants
- Likely pathogenic variants

According to **ACMG criteria**, in genes with:

- Definitive
- Strong
- Moderate

evidence of association with dilated cardiomyopathy (ClinGen classification)

Genes included:

BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN, DSP, ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1, VCL.

To be considered negative, the test must also **not contain variants of uncertain significance (VUS)** that could potentially be reclassified as pathogenic during the study.

These will be defined as **Hot VUS** if they meet ACMG criteria:

- 1 Strong + 1 Supporting OR
- 2 Moderate + 1 Supporting OR
- 1 Moderate + 3 Supporting

All genetic studies will be centrally reviewed by at least one cardiologist specialized in cardiovascular genetics.

Safe withdrawal of neurohormonal therapy

If the withdrawal strategy is safe during the first 6 months, follow-up will continue to 12 months.

Withdrawal will be considered **safe** if it is not associated with:

- Occurrence of the primary endpoint
- Sustained ventricular arrhythmias
- ICD shocks

DATA COLLECTION VARIABLES

Demographic data

- Date of birth
- Sex
- Race
- Weight
- Height

Cardiac history

- Family history:
  - Non-ischemic cardiomyopathy
  - Other cardiomyopathies
  - Sudden cardiac death
  - Myopathy
- Date of NICM diagnosis
- Pre-CRT echocardiographic data:
  - LVEF
  - LV end-systolic and end-diastolic volumes
  - Mitral regurgitation grade
  - Left atrial size
  - Pulmonary artery pressure
- CRT implantation:
  - Date
  - Device type (pacemaker/ICD)
  - Type of pacing (biventricular / left bundle branch area)
- Post-CRT echocardiographic data (≥6 months):
  - LVEF
  - LV volumes
  - Mitral regurgitation
  - Left atrial size
  - Pulmonary artery pressure

Other medical history

- Hypertension
- Diabetes mellitus
- Dyslipidemia
- Atrial fibrillation (type)
- Comorbidities (Charlson index)

CRT device interrogation

- Atrial and ventricular pacing percentage
- Activity sensor (R) on/off
- Pacing mode (DDD or VVI)
- AV delay (paced and sensed)
- Pacing configuration
- Supraventricular arrhythmias
- Ventricular arrhythmias
- Device therapies (appropriate/inappropriate)

Echocardiography variables

- Date
- Blood pressure and heart rate
- Rhythm
- LVEF (biplane)
- LV diameters and volumes
- Mechanical dyssynchrony parameters:
    - Pre-ejection interval differences
    - Septal vs posterior wall timing
    - Radial strain delay
- Strain parameters:
    - Global longitudinal strain
    - Peak strain dispersion
- Myocardial work:
    - GWI, GCW, GWW, GWE
- Other:
    - Apical rocking
    - TAPSE
    - Left atrial size and volume
    - Diastolic function parameters (E, A, E’)
- Valve disease:
    - Aortic stenosis/regurgitation
    - Mitral regurgitation
    - Tricuspid regurgitation

- Pulmonary artery pressure
- Pericardial effusion

Treatment

Neurohormonal therapy

- Beta-blockers
- ACE inhibitors
- ARBs
- ARNI
- Mineralocorticoid receptor antagonists
- SGLT2 inhibitors

(Drug name and dose recorded)

Other drugs

Includes:

- Thiazide diuretics
- Calcium channel blockers
- Nitrates
- Ivabradine
- Digoxin
- Antiarrhythmics
- Antidiabetics
- Statins
- Antiplatelets
- Anticoagulants
- Proton pump inhibitors

ECG variables

- Rhythm
- Heart rate
- Paced QRS duration

For left bundle branch pacing:

- Stimulus-to-R peak in V6
- R wave in V1
- Timing differences V1–V6
- Pacing type

Laboratory variables

- Hematocrit
- Ferritin
- Transferrin saturation
- Creatinine
- Urea
- GFR
- Sodium
- Potassium
- NT-proBNP
- Troponin
- CK
- CK-MB

Clinical follow-up

- NYHA class
- Physical examination findings
- Quality of life
- Patient-reported status
- Interventions performed:
    - AF ablation
    - Ventricular ectopy ablation
    - Antiarrhythmic initiation

Cardiovascular adverse events

- Heart failure treated outpatient
- ED/day hospital visits
- HF hospitalizations
- Acute coronary syndrome
- Other cardiac admissions
- Death and cause

Additional data (echo, ECG, device, NT-proBNP) may be collected during events.

Visits of the study

	Screening (max 30 días)	Inclusion and randomization	Withdrawal of heart failure treatment/control	Post withdrawal visit (or 10 weeks after inclusion in control group)	Phone visits 16 and 20 months after randomization	6 months visit	9 months visit	Final visit 12 months
Informed consent	X							
Elegibility criteria	X	X						
Demographic and clinical data	X							
ECG	X					X		X
Echo	X					X		X
CRT check	X					X		X
Blood sample analysis	X			X	X	X	X	X
Clinical visit	X			X		X	X	X
Phone visit			X	X				
Record of medication	X	X	X	X	X	X	X	X
Record of adverse events			X	X	X	X	X	X

STUDY DURATION AND PHASES

The duration of the study until completion of follow-up for the primary endpoint will be **12 months**, including:

- 6 months for patient recruitment
- 6 months for follow-up

To assess secondary endpoints that include 12-month follow-up, the **total study duration will be 18 months**, and the study will be considered completed when the last patient completes the 12-month follow-up visit after inclusion.

DATA STORAGE

The study master file will be retained for at least **25 years** after completion of the study, in accordance with **Royal Decree 1090/2015**.

PROSPECTIVE REGISTRY AFTER COMPLETION OF THE CLINICAL TRIAL

If the primary objective is achieved, patients will be offered continued clinical follow-up for an additional **two years** within a prospective registry.

- Patients in the **intervention group**, unless they have reached the primary endpoint, will remain **off neurohormonal therapy**
- Patients in the **control group** will undergo **withdrawal of neurohormonal therapy**, following the same protocol as in the clinical trial

Before initiating withdrawal in control group patients:

- A summary of the results obtained in the intervention group will be submitted to the Ethics Committee (CEIm)
- A protocol amendment will be submitted

ETHICAL AND DATA PROTECTION ASPECTS

The study will be conducted in accordance with:

- National and international ethical guidelines
- The **Declaration of Helsinki**
- Data protection regulations (**Organic Law on Data Protection 03/2018**)

Before inclusion:

- All patients will receive a detailed explanation of the protocol

- A patient information sheet
- The informed consent document

Patients will be given sufficient time to read, understand, and approve participation.

During the study:

- Patient data will be **coded and anonymized**
- Confidentiality will be strictly maintained

Participation is entirely voluntary, and patients may withdraw at any time without any impact on their standard clinical care.

If a patient withdraws consent:

- They will have the right to request deletion of their data

Data storage will cease upon study completion.

Data management

Patient data will be stored in an electronic database created using **REDCap® (Vanderbilt University, Nashville, TN, USA)**.

- Patients will be identified only by their inclusion number
- Data collected will include:
    - Clinical
    - Echocardiographic
    - Electrocardiographic
    - Laboratory variables

All data will be coded as numerical variables for analysis.

The **principal investigator** will have access to the full database during the study.

Intellectual property

The intellectual property of the study results belongs to the **principal investigator, Dr. Andrea Di Marco**.

Regulatory compliance

The study will be conducted:

- Strictly according to this protocol
- In accordance with **EU Regulation 536/2014**
- Following **Good Clinical Practice (GCP)** principles

PATIENT SAFETY

The **STOP-CRT** trial demonstrated that withdrawal of beta-blockers and ACE inhibitors in CRT super-responders is safe and not associated with serious adverse events.

In another context of recovered LVEF after reversible ventricular dysfunction, the **WITHDRAW-AF** trial showed that complete withdrawal of neurohormonal therapy is safe.

In the present study, a highly selected subgroup of patients is included:

- Whose only documented cause of LV dysfunction was electrical dyssynchrony due to LBBB
- Who have recovered normal LV function after CRT
- Who are clinically stable

In this context, withdrawal of neurohormonal therapy is expected to be safe.

Nevertheless:

- A **liability insurance policy** will be contracted to cover any potential harm to patients
- An **interim safety analysis** will be performed after completion of therapy withdrawal in the first **16 patients**

INFORMATION TO INVESTIGATORS

The sponsor will provide investigators with any safety-related information that may impact patient safety as soon as possible.

Investigators will be continuously informed throughout the study regarding:

- Safety issues
- Protocol modifications related to safety