

# Clinical and Preclinical Heart Failure Research Network (REDINSCOR). Instituto de Salud Carlos III Cooperative Special Topic Research Networks

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Heart failure is a prevalent condition that is associated with high morbidity and mortality and that places a substantial demand on healthcare resources. As the condition often affects older individuals with comorbidities, its treatment requires the implementation of an integrated model of care that can be applied in primary care, in hospitals, and in the patient's home. The use of heart failure units has improved quality of life in these patients and has reduced hospital admissions. However, in Spain integrated care has not yet been widely implemented. Clinical and preclinical research on heart failure is complex and, consequently, it is essential for investigators to work together in research networks. As a result, 16 Spanish centers have organized themselves into a heart failure research network (REDINSCOR). This network is considering the establishment of a national heart failure registry and is involved in seven research projects, whose subjects range from molecular biology and cell physiology to diagnosis, treatment, and the development of integrated healthcare models.

**Key words:** Heart failure. Heart failure units. Research networks.

## Red de investigación clínica y básica en insuficiencia cardíaca (REDINSCOR). Redes temáticas de investigación cooperativa del Instituto de Salud Carlos III

La insuficiencia cardíaca es una enfermedad prevalente asociada a elevadas morbilidad y necesidad de recursos sanitarios. Incide frecuentemente en población de edad avanzada con múltiples enfermedades y su atención requiere un modelo organizativo transversal entre la asistencia primaria, el hospital y el domicilio del paciente. Las unidades de insuficiencia cardíaca han mejo-

rado la calidad de vida y han reducido los ingresos hospitalarios de estos pacientes. Sin embargo, en España la implantación de un modelo de atención transversal todavía no se ha generalizado. La investigación clínica y básica sobre esta enfermedad es compleja y requiere una estrategia científica basada en el trabajo en red.

A tal efecto, 16 centros de nuestro país se han organizado en una red de investigación centrada en la insuficiencia cardíaca (REDINSCOR) que incluye un registro clínico nacional y 7 subproyectos que van desde la biología molecular y la fisiología celular al diagnóstico, el tratamiento y el desarrollo de modelos transversales de atención sanitaria.

**Palabras clave:** Insuficiencia cardíaca. Unidades de insuficiencia cardíaca. Redes de investigación.

## INTRODUCTION

Heart failure, the end stage of many cardiovascular diseases, is a common, severe condition that places a great demand on health care resources. In Europe, heart failure is estimated to affect approximately 10 million individuals, and the incidence increases with increasing age (1% of the population over 40 and 17% of those over 85 years of age).<sup>1,2</sup> It has an associated mortality of 50% at 5 years after the diagnosis,<sup>3,4</sup> is the reason for 5% of all hospitalizations in Spain, and consumes 2% of the country's total healthcare expenditure.

In recent years, the clinical and prognostic characterization of heart failure has improved greatly because of the availability of advanced echocardiography techniques, new biomarkers (eg, natriuretic peptides,<sup>5-7</sup> troponins,<sup>8</sup> ultrasensitive C-reactive protein [CRP],<sup>9</sup> and adiponectin<sup>10</sup>), new drug treatments, and complex cardiac pacing devices.<sup>11-13</sup> In the field of genetics, important advances have been made in the identification of at-risk phenotypes.<sup>14-16</sup>

Nevertheless, prognostic stratification of this condition should be improved through the development of new

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scores to identify patients at a high risk of death due to cardiovascular causes. In addition, the use of health care resources should be optimized and allocated according to the patient's risk profile; hence, cardiovascular risk should be established as accurately as possible. The growing spectrum of new therapeutic approaches in such a severe disease requires precise identification of patients who will respond to, and benefit from, treatment.

Comprehensive treatment of a patient with heart failure requires coordination among the various components of the public health care system, which form a continuum that includes primary care, specialized care, hospital emergency systems and clinical units, and home care. There is a need for disease prevention programs, and the means to achieve early diagnosis, coordinated activity, and equitable access to health care for all patients. Heart failure units have a decisive impact on maintaining patients in a clinically stable state, improving their quality of life and optimizing the use of health care resources.

Hospitals in Spain have developed models of heart failure units that differ in complexity according to the available resources and local health care organization.<sup>17</sup> In most cases, however, these models are not effectively coordinated with primary care, and this results in fragmentation of the health care process. Home care and palliative care are important for patients with end-stage heart failure,<sup>18</sup> although this type of assistance has not received systematic attention in our country. Heart transplantation programs, created in Spain in 1984, have extended to various hospitals, facilitated by the relatively high rate of organ donation in our country. The morbidity and mortality of heart transplant recipients is still high and because of the limited availability of organs, only a small portion of the large patient population has access to this effective therapeutic option. Sudden death and death due to heart failure refractory to treatment are the main causes of mortality in patients with heart failure and depressed left ventricular function, but the pattern of mortality in patients with preserved systolic function is less well characterized. Moreover, the therapeutic strategy for heart failure patients with normal systolic function is still not completely defined and, therefore, requires specific clinical studies for this purpose.

## RATIONALE

The available information on heart failure in Spain is highly fragmented, since it proceeds from series of hospitalized patients, small patient cohorts, and studies with short follow-up periods. In addition, initiatives aimed at the development of comprehensive community care programs for heart failure are only partially consolidated in some areas of the country.

REDINSCOR was conceived as an interdisciplinary, collaborative, scientific network that would provide a solid platform for clinical and preclinical research on heart failure in Spain. In addition to the scientific aspects,

REDINSCOR attempts to generate useful epidemiological information for the Sistema Nacional de Salud (SNS, National Healthcare System) regarding efficient and fair use of therapeutic resources.

## OBJECTIVES AND STRATEGIC PLAN

The goal of the REDINSCOR network for research in heart failure is to expand our current knowledge of the mechanisms, clinical diagnoses, risk markers, health care models, and treatment of heart failure patients in Spain. To achieve these aims, a strategic plan has been designed, based on a set of clinical and preclinical research projects that focus on heart failure. These projects are structured as a collective central project and 7 specific subprojects that encompass relevant problems related to the disease. The interaction of each participating group in one or more of these proposed projects yields an intersecting scientific grid that justifies conducting the studies within a research network. An outline of the structure of the REDINSCOR Strategic Plan is shown in Figure 1.

## CENTRAL PROJECT

The central project consists of a registry for clinical and prognostic characterization of heart failure in Spain with equal participation of all the institutions in the network, distributed in 7 autonomous communities. More than half the participating centers have an active heart transplantation program.

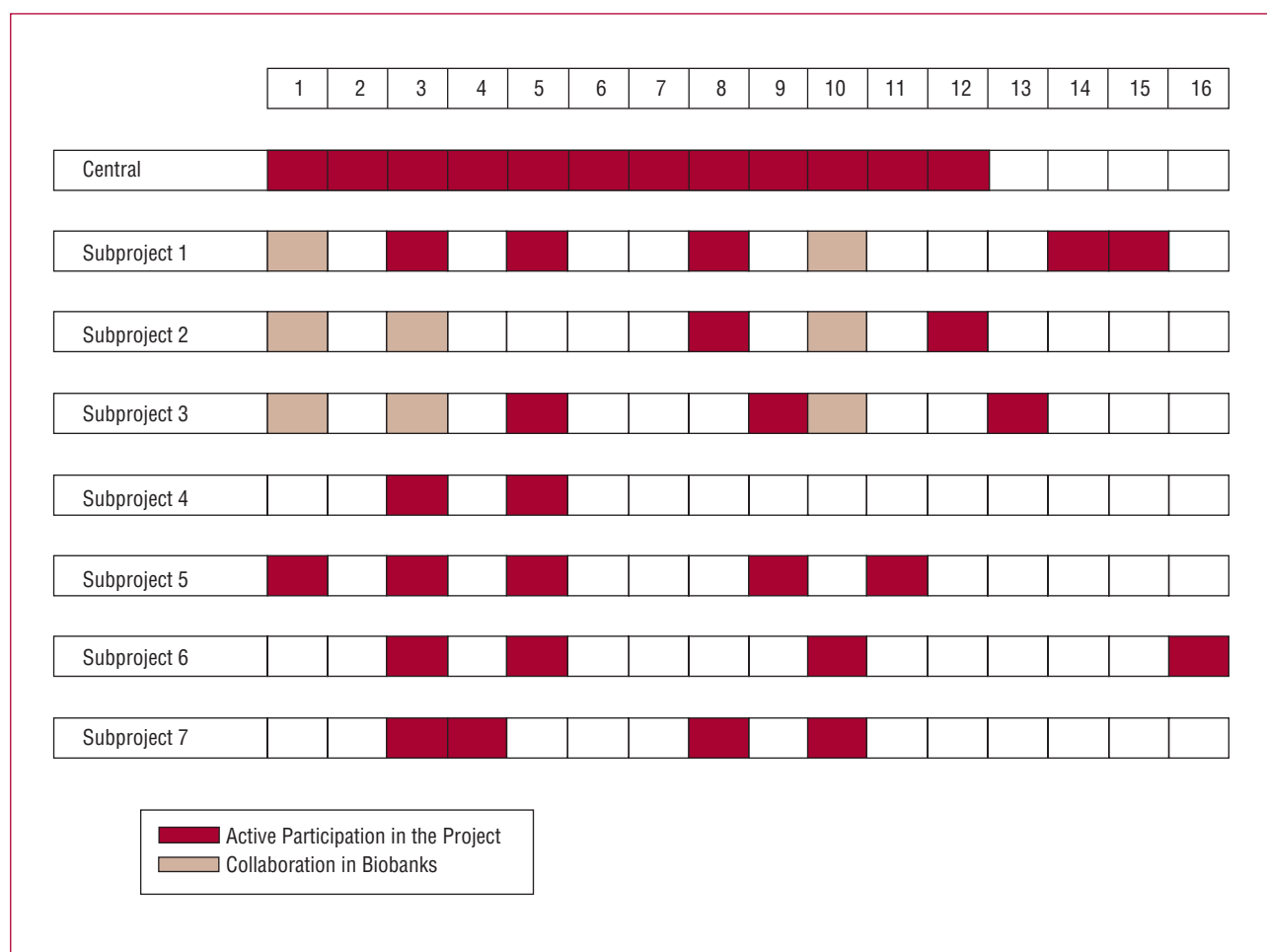
The overall purpose of the project is to investigate the clinical and epidemiological patterns (mortality, morbidity, hospitalizations), causes of death, and pattern of clinical instability experienced by heart failure patients, including those with depressed systolic function as well as those with preserved systolic function. The project design is contemplated as a prospective, cohort study with a 4-year follow-up and cross-sectional assessment every 6 months that includes patients over 18 years old with class II, III, or IV heart failure. The data are uploaded to the network website ([www.redinscor.org](http://www.redinscor.org)).

## SUBPROJECTS

The subprojects are a set of research proposals within the groups in the network that include various aspects of heart failure (pathophysiology, signs, and symptoms, diagnosis, and treatment). The subprojects attempt to address specific hypotheses through the use of competitive methods, and are themselves an opportunity for scientific exchange and researcher training among the various centers.

### Subproject 1. Molecular Basis of Heart Failure

This study involves a set of tasks focused on the following: *a*) investigate cell types and cell mediators



**Figure 1.** Schematic diagram depicting the participation of the various centers comprising the research project network. Identification of the centers: 1: Hospital Universitario Virgen de Valme, Seville; 2: Hospital Insular de Las Palmas de Gran Canaria; 3: Hospital Clínico Universitario, Barcelona; 4: Gerencia del Ámbito Territorial de Bcelona-ICS; 5: Hospital de la Santa Creu i de Sant Pau, Barcelona; 6: Hospital Universitario Arnau de Vilanova, Lleida; 7: Hospital Universitario Joan XXIII, Tarragona; 8: Hospital Clínico Universitario, Santiago de Compostela; 9: Hospital Clínico San Carlos, Madrid – Instituto Cardiovascular; 10: Hospital 12 de Octubre, Madrid; 11: Clínica Puerta de Hierro, Madrid; 12: Hospital Universitario Virgen de la Arrixaca, Murcia; 13: Hospital Clínico, Valencia; 14: Hospital Clínico San Carlos, in Madrid –Internal Medicine; 15: Institut Català de Ciències Cardiovasculars; 16: Universitat Politècnica de Catalunya

implicated in the ventricular modeling occurring in heart failure, performed in explanted hearts of transplant patients; *b*) study the pathways related to endoplasmic reticulum stress in cardiomyocytes of patients with heart failure; *c*) investigate the evolution of proinflammatory cytokine concentrations (tumor necrosis factor alfa [TNF $\alpha$ ], interleukin [IL] 1, IL-6, and IL-2) during the development of heart failure in an experimental model of hypertensive rats; and *d*) study gene and protein expression in cardiac tissue specimens from heart failure patients.

### Subproject 2. Implication of Cardiac Fat in the Pathophysiology of Heart Failure

This subproject attempts to: *a*) determine epicardial fat content by echocardiography and investigate whether

there is a correlation between this factor and parameters of diastolic function, ventricular dilation, and circulating natriuretic peptides, and adipocytokines; *b*) determine the expression of resistin, leptin, and adiponectin in epicardial and subcutaneous adipose tissue of patients with heart failure, and investigate correlations between these factors and obesity, and diabetes mellitus; and *c*) observe the activity of NO synthetase in cardiomyocytes of the study patients.

### Subproject 3. Electrophysiological Effects of Mechanical Stress on Myocardial Tissue

This goal of this project is to increase our understanding of the pathophysiology of mechanical stress. The following tasks will be carried out: *a*) determine the role of mechanical stress in the

expression and function of receptors that activate protein kinase A-mediated phosphorylation in human cardiomyocytes and its implication in intracellular calcium regulation; *b*) characterize the effects of acute mechanical stress on intracellular calcium regulation in human cardiomyocytes; *c*) determine the electrophysiological effects of acutely elevated intra-atrial pressure in the normal heart and in heart failure; *d*) analyze the effects of ventricular myocardial stretch and stretch receptor blockade on electrophysiological parameters in isolated, perfused rabbit heart; and *e*) analyze with optical mapping the electrophysiological effects induced in the cell and in intracellular calcium flow by mechanical stress and stretch receptor blockade in isolated pig heart.

#### **Subproject 4. Ablation of Atrial Fibrillation in Heart Failure**

This clinical study will attempt to: *a*) assess whether there are differences in the number of recurrences of atrial fibrillation in patients with left ventricular systolic dysfunction; and *b*) evaluate whether there is an improvement and lower risk of complications in patients who maintain sinus rhythm as compared to those with recurrent arrhythmia.

#### **Subproject 5. Efficacy of Ventricular Resynchronization in Heart Failure**

The following are the aims of this study: *a*) assess the effects of cardiac resynchronization on functional capacity, quality of life, and inverse cardiac remodeling, comparing the results obtained in patients with sinus rhythm to those of patients presenting atrial fibrillation; and *b*) compare the effects of cardiac resynchronization according to the site of right ventricular stimulation.

#### **Subproject 6. Myocardial Bioimpedance, a New Tool for the Diagnosis of Heart Graft Rejection**

The objective of this study is to develop a new noninvasive diagnostic technique to detect post-transplantation heart graft rejection in humans, based on transesophageal electrode catheter measurement of myocardial impedance.

#### **Subproject 7. Continuing Care Models in Heart Failure**

This study focuses on developing a cross-sectional care model encompassing all facets of health care for comprehensive treatment of heart failure, as well as training for the professionals involved in this activity, that will be applicable to all centers in the network.

## **ORGANIZATIONAL PLAN**

### **Groups Comprising the Network**

The groups that form the REDINSCOR network have joined together voluntarily to create a scientific platform focused on heart disease with extensive geographic representation within Spain. Taking into account the fact that acquisition of scientific knowledge on heart failure requires a multidisciplinary approach, some of the researchers involved have a clinical profile and others—an important part—are basic researchers with several areas of expertise, such as molecular biology, proteomics, genetics, cell electrophysiology, biochemistry, bioengineering, epidemiology, statistics, and computing. Cell regeneration is not an objective of the network in this effort, since there are several major basic research structures in our country focused on cell regeneration. Nonetheless, REDINSCOR will have considerable clinical potential to collaborate and develop projects in regenerative medicine in future efforts.

A list of the 16 centers located in 7 autonomous communities that comprise the REDINSCOR network is provided in the Appendix.

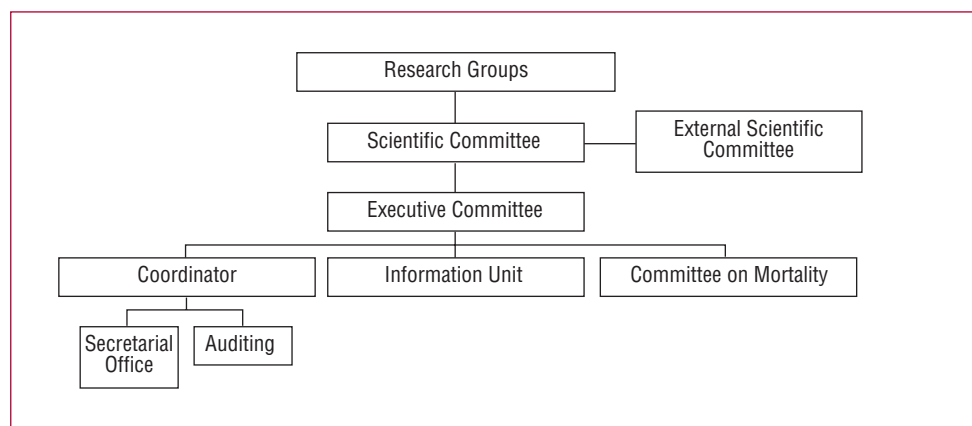
### **Organizational Structure**

To ensure adequate representation among the groups participating in the network, as well as ethical scientific management, REDINSCOR has the following internal committees (Figure 2):

*Scientific Committee.* The Scientific Committee is the main representational body of the network and is comprised of all the principal investigators from each group. The Scientific Committee appoints the members of the Executive Committee and the coordinator, approves new research proposals, oversees ethical, and legal aspects, approves the policy regarding publications, and directs the relationships with other research groups, institutions, or businesses. The Scientific Committee has 1 ordinary meeting per year during the Annual Scientific Meeting of the network, and will hold extraordinary meetings when the circumstances require it or at least one-third of the members request a meeting.

*Executive Committee.* The Executive Committee is comprised of 9 persons, elected from among the members of the Scientific Committee. Their task is to propose new projects and activities for the network and design the content of the Annual Scientific Meeting.

*Information Unit.* The Information Unit is a support body for the network, comprised of a coordinator, database administrator, epidemiologist, and statistician. Its responsibilities include the design and maintenance of the database, control of the quality and accuracy of the information, and compliance with the Spanish Privacy and Data Protection Act.



**Figure 2.** Organizational chart of REDINSCOR

**Committee on Mortality and case-closure.** The network coordinator, the epidemiologist and statistician in charge of the Information Unit, and 3 investigators elected from among the members of the Scientific Committee comprise the Committee on Mortality and case-closure. The task of these professionals is to analyze the cases of death and classify the cause of death according to the criteria established in the scientific report. The committee resolves any conflict regarding closure of cases included in the study and cases lost to follow-up.

**External Scientific Committee.** The External Scientific Committee is composed of a group of internationally renowned investigators in the area of heart failure and cardiovascular research in general. These experts will act as outside scientific consultants for the network.

## Common Platforms

### Database

The database is the tool used to store data from all the groups comprising the network and includes the mandatory baseline variables common to all the studies included in the network. The database is available on the Internet ([www.redinscor.org](http://www.redinscor.org)), and contains a management module for online statistics and a report generator.

### Biobanks

**Cardiac and aortic vascular tissue obtained in vivo.** These samples include atrial and ventricular myocardial tissue specimens obtained during cardiac surgery, and which are usually discarded. The atrial tissue is obtained during cannulation of the atrium prior to extracorporeal circulation. The ventricular tissue is papillary muscle removed during mitral valve surgery or myectomy in surgery for hypertrophic cardiomyopathy. Aortic tissue is obtained during repair surgery for the ascending aorta. These specimens can be used in studies on the physiology of isolated myocytes or stored for genetic or molecular biology studies.

**Cardiac tissue obtained from explanted organs.** These specimens are obtained from the explanted hearts of patients receiving a heart transplant. A common pathological anatomy extraction protocol has been established for all network centers with an active heart transplantation program. To ensure the effectiveness of this program, the extraction, storage, and distribution of these specimens will be carried out by the investigation staff directly involved in the network.

**Biological samples.** These include samples of blood and other biological fluids that will be used in research by the network. These samples will be stored at the sites promoting the specific research project.

## CONCLUSIONS

REDINSCOR is a platform for clinical and basic research in heart failure at the national level, including 16 centers distributed in 7 autonomous communities. The scientific strategic plan consists of a central project involving a national registry, and 7 subprojects focused on sectorial aspects of heart disease, ranging from molecular biology and cell physiology to diagnosis and treatment, as well as the development of cross-sectional care models for patients with heart failure. Researcher training and mobility, and the exchange of knowledge are all essential objectives of the network.

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## APPENDIX

List of centers and principal investigators participating in REDINSCOR:

1: Hospital Universitario Virgen de Valme, Seville (Rafael Vázquez); 2: Hospital Insular de Las Palmas de Gran Canaria (Vicente Nieto); 3: Hospital Clínico Universitario, Barcelona (Josep Brugada); 4: Gerencia del Àmbit Territorial de Barcelona ICS (Iskra Ligüerre); 5: Hospital de la Santa Creu i de Sant Pau, Barcelona (Juan Cinca); 6: Hospital Universitario Arnau de Vilanova, Lleida (Fernando Worner); 7: Hospital Universitario Joan XXIII, Tarragona (Alfredo Bardají); 8: Hospital Clínico Universitario, Santiago de Compostela (José Ramón González Juanatey); 9: Hospital Clínico San Carlos, Madrid – Internal Medicine (Arturo Fernández-Cruz); 10: Hospital 12 de Octubre, Madrid (Carlos Sáenz de Calzada); 11: Clínica Puerta de Hierro, Madrid (Luis Alonso Pulpón); 12: Hospital Universitario Virgen de la Arrixaca, Murcia (Mariano Valdés); 13: Hospital Clínico, Valencia (Francisco Javier Chorro); 14: Hospital Clínico San Carlos, – Instituto Cardiovascular (Julián Pérez Villacastín); 15: Institut Català de Ciències Cardiovasculars (Concepción Vicenta Llorente); 16: Universitat Politècnica de Catalunya (Francisco Javier Rosell)

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