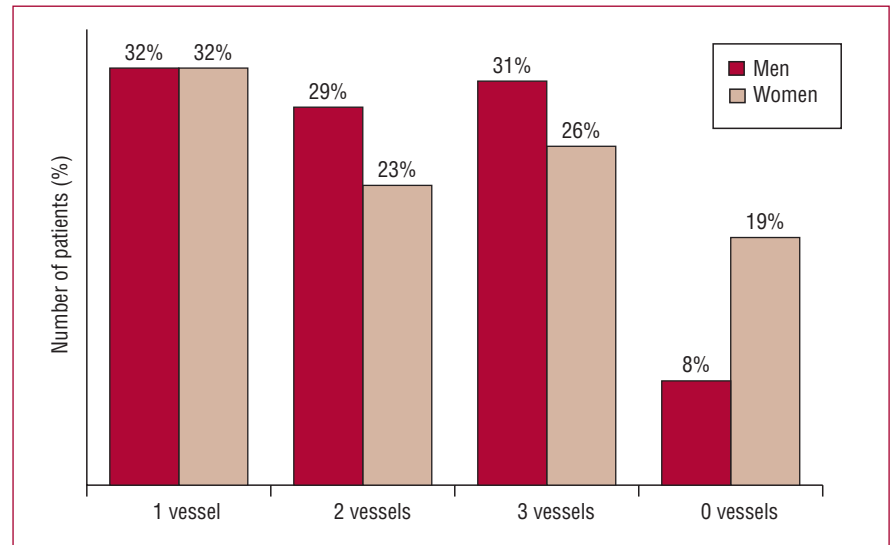




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CARDIOVASCULAR DISEASE IN WOMEN. A STUDY INTO THE CURRENT SITUATION IN SPAIN

Coordinators: Dr. Manuel Anguita and Dra. Eulàlia Roig

Preface

Alberto Infante Campos

Introduction

Manuel Anguita et al

Abbreviations

Methodology Employed in the Study of Cardiovascular Disease in Women in Spain

Manuel Anguita et al

Influence of Sex on Acute Coronary Syndrome Mortality and Treatment in Spain

Joaquín Alonso et al

Heart Failure in Women: Sex Differences in Spain

Manuel F. Jiménez-Navarro et al

Hypertension in Spanish Women: Analysis of Data Collected by the Spanish Society of Cardiology Section of Arterial Hypertension

Pilar Mazón et al

1D Atrial Fibrillation in Women: An Analysis of the Situation in Spain

Julián Pérez-Villacastín et al

38D

2D Valvular Heart Disease in Women: Sex Differences in Spain

Juan J. Gómez-Doblas

42D

3D Influence of Sex on Heart Transplantation Mortality: Data From the Spanish National Heart Transplantation Registry

Luis Almenar, on behalf of Spanish
Heart Transplant Teams

49D

4D A Study of Cardiovascular Disease in Women in Spain: Conclusions and Final Recommendations

Manuel Anguita et al

55D

30D

REVISTA ESPAÑOLA DE CARDIOLOGIA

SUPLEMENTOS

VOLUME 8, FASCICLE D, 2008

CARDIOVASCULAR DISEASE IN WOMEN. A STUDY INTO THE CURRENT SITUATION IN SPAIN

Coordinators: Dr. Manuel Anguita and Dra. Eulàlia Roig

Preface Alberto Infante Campos	1D	Atrial Fibrillation in Women: An Analysis of the Situation in Spain Julián Pérez-Villacastín and Silvia del Castillo	38D
Introduction Manuel Anguita and Eulàlia Roig	2D	Valvular Heart Disease in Women: Sex Differences in Spain Juan J. Gómez-Doblas	42D
Abbreviations	3D	Influence of Sex on Heart Transplantation Mortality: Data From the Spanish National Heart Transplantation Registry Luis Almenar, on behalf of Spanish Heart Transplant Teams	49D
Methodology Employed in the Study of Cardiovascular Disease in Women in Spain Manuel Anguita, Joaquín Alonso, Vicente Bertomeu, Juan J. Gómez-Doblas, Ramón López-Palop, Milagros Pedreira, Julián Pérez-Villacastín, and Eulàlia Roig	4D	A Study of Cardiovascular Disease in Women in Spain: Conclusions and Final Recommendations Manuel Anguita, Joaquín Alonso, Vicente Bertomeu, Juan J. Gómez-Doblas, Ramón López-Palop, Milagros Pedreira, Julián Pérez-Villacastín and Eulàlia Roig	55D
Influence of Sex on Acute Coronary Syndrome Mortality and Treatment in Spain Joaquín Alonso, Héctor Bueno, Alfredo Bardají, Xavier García-Moll, Xavier Badía, Miquel Layola, and Ágata Carreño	8D		
Heart Failure in Women: Sex Differences in Spain Manuel F. Jiménez-Navarro and Manuel Anguita-Sánchez	23D		
Hypertension in Spanish Women: Analysis of Data Collected by the Spanish Society of Cardiology Section of Arterial Hypertension Pilar Mazón and Vicente Bertomeu	30D		

The cover image is from the article by Alonso J et al, published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA SUPLEMENTOS. Data on the extension of coronary disease in the group of men and women with acute coronary syndrome without ST segment elevation who underwent cardiac catheterism.

This publication shows the conclusions, findings and comments of the authors and mentions clinical studies that could have indications/dosages/administration forms of currently unauthorized medicinal products in Spain. It is stressed that any drug mentioned should be used in accordance with the Data Sheet in force in Spain.

REVISTA ESPAÑOLA DE CARDIOLOGÍA SUPLEMENTOS

VOLUMEN 8, FASCÍCULO D, 2008

ENFERMEDAD CARDIOVASCULAR EN LA MUJER. ESTUDIO DE LA SITUACIÓN EN ESPAÑA

Coordinadores: Dr. Manuel Anguita y Dra. Eulàlia Roig

Prólogo Alberto Infante Campos	1D	Fibrilación auricular en la mujer: análisis de la situación en España Julián Pérez-Villacastín y Silvia del Castillo	38D
Introducción Manuel Anguita y Eulàlia Roig	2D	Válvulopatías en la mujer: diferencias de sexo en España Juan J. Gómez-Doblas	42D
Abreviaturas	3D		
Diseño general del proyecto de estudio sobre la situación de la enfermedad cardiovascular de la mujer en España Manuel Anguita, Joaquín Alonso, Vicente Bertomeu, Juan J. Gómez-Doblas, Ramón López-Palop, Milagros Pedreira, Julián Pérez-Villacastín y Eulàlia Roig	4D	Influencia del sexo en la mortalidad por trasplante cardiaco: subanálisis del Registro Español de Trasplante Cardiaco Luis Almenar, en representación de los Grupos Españoles de Trasplante Cardiaco	49D
Influencia del sexo en la mortalidad y el manejo del síndrome coronario agudo en España Joaquín Alonso, Héctor Bueno, Alfredo Bardají, Xavier García-Moll, Xavier Badia, Miquel Layola y Ágata Carreño	8D	Proyecto de estudio sobre la situación de la enfermedad cardiovascular en la mujer en España: conclusiones y recomendaciones finales Manuel Anguita, Joaquín Alonso, Vicente Bertomeu, Juan J. Gómez-Doblas, Ramón López-Palop, Milagros Pedreira, Julián Pérez-Villacastín y Eulàlia Roig	55D
Insuficiencia cardiaca en la mujer. Diferencias de sexo en España Manuel F. Jiménez-Navarro y Manuel Anguita-Sánchez	23D		
Hipertensión arterial en la mujer en España: análisis de los registros de la Sección de Hipertensión Arterial de la Sociedad Española de Cardiología Pilar Mazón y Vicente Bertomeu	30D		

La imagen de la portada procede del artículo de Alonso J et al, publicado en este número de la REVISTA ESPAÑOLA DE CARDIOLOGÍA SUPLEMENTOS. Datos sobre la extensión de la enfermedad coronaria en el grupo de varones y mujeres con SCASEST a los que se realizó cateterismo cardiaco.

Esta publicación refleja conclusiones, hallazgos y comentarios propios de los autores y se mencionan estudios clínicos que podrían contener indicaciones/posologías/formas de administración de productos no autorizadas actualmente en España. Se recuerda que cualquier fármaco mencionado deberá ser utilizado de acuerdo con la ficha técnica vigente en España.

Preface

Alberto Infante Campos

General Director of the Quality Agency of the SNS. Ministry of Health. Madrid. Spain.

In March 2006, the Ministry of Health introduced the Quality Plan for the National Health System. The Quality Plan aims to respond to issues that affect the great principles and challenges of our health system. Its objectives have concentrated in areas and projects of action that were developed in 2006 and 2007 in cooperation with scientific and professional societies. The work presented in this supplement is included in this framework.

The Quality Plan aims to ensure the highest quality health care to all citizens and to provide useful tools to professionals and those responsible for the health of the autonomous communities. Thus, the Ministry of Health complies with its coordination role within the National System of Health, strengthening cohesion and ensuring equity in access and quality of offered benefits.

Within the field of medicine, knowledge evolves rapidly. This is evident in trends in recent decades regarding advances in knowledge of the causes of diseases, their diagnoses and treatments, as well as the prevention of their recurrence. In light of this, health professionals are required to constantly update knowledge and to critically analyse advances in order to make informed decisions on what should be incorporated into clinical practice and how.

The promotion of consensus formulation and collaborative development of health strategies are carried out to promote quality health care and provide common frameworks for clinical decisions. Such promotion comprises measures to foster the clinical excellence of practitioners and good planning of the public health organisation.

Equity in health care is a priority of the National System of Health, as established by the General Health Act of 1986. In Spain, there is a tradition of studying the relationship between social determinants and health outcomes. However, studies on the role of health inequities in health systems remain scarce.

To contribute to this knowledge, the Ministry of Health is supporting the development of various research, studies and reports that provide information on improving equity in the health system. Examples of this are the inclusion of a specific line of equity in the Carlos III Health Institute research requests and in the Quality Awards in the National System of Health or the completion and publication of the annual reports 'Health and Gender'.

Although inequalities in the health and care of men and women by health services affect all, they cause more harm to women for various reasons, both social and organisational.

Achieving equity in health between the genders requires that men and women be treated equally when their needs are the same, but also that their different needs be addressed in a differentiated manner. This must be taken into account throughout the process of the planning and delivery of services, in all areas and at all levels of the system.

It is also essential to disseminate the correct information about different people's health and about the sanitation performance for each of them. In this sense, disaggregating data by gender is the basis of useful knowledge for decision-making without gender biases concerning the health systems and the promotion of equity within health systems.

This supplement is the result of the collaboration of professionals and authorities in a mutual framework for improving the quality and equity of health, especially in terms of gender equity. A job analysis of existing records has been conducted, where this is a result of the effort to improve clinical excellence among professionals.

This critical analysis is an important commitment of the Spanish Society of Cardiology, and will certainly contribute to the quality, equity and improvement of women's health.

Introduction

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The present *Spanish Journal of Cardiology* supplement presents the results of a project that was initiated two years ago by the Agency of Research of the Spaniard Cardiology (*Agencia de Investigación de la Sociedad Española de Cardiología or SEC*) at the behest of its Executive Committee. As noted in the initial article in this supplement, cardiovascular diseases are currently the most important cause of mortality in Western countries, for both men and women. However, women's risk for these diseases is underestimated significantly due to the perception that women are "protected" from ischemic heart disease. This false perception of reduced risk that exists not only among women, but also among health professionals, can lead to less appropriate care (both from a diagnostic and therapeutic point of view) of cardiovascular disease in women. This is relevant not only in the field of ischemic heart disease management, but also in various other fields. In recent years, health authorities and scientific societies have developed various campaigns in an attempt to improve knowledge on these issues and raise awareness about the importance of cardiovascular disease in women¹.

Although publications on some aspects of cardiovascular disease in women have been created in our country, there is a lack of complete and systematised information on potential differences related to gender in various cardiac pathologies. Therefore, the SEC, with the sponsorship and funding of the Centre of the Health of Women of the Ministry of Health research agency, began a study on the care and management of major cardiovascular disease in women in Spain, including the analysis of differences between men and women.

First, the study aims to collect available data that could provide reliable conclusions on different selected pathologies. Second, an analysis of existing data was conducted in relation to gender to reveal

possible differences between men and women in terms of clinical features, diagnosis and therapeutic management and prognosis. Third, the aspects for which there are currently insufficient sources of information were labelled, and possible projects proposed to resolve these deficits. Finally, a final report with conclusions of the study and recommendations for improving the attention to women with cardiovascular disease in Spain was prepared.

Since there are numerous cardiovascular diseases and it would be impossible to cover them all in a project of this type, major heart diseases were selected by their prevalence and prognosis severity. Acute coronary syndrome, heart failure (including cardiac transplant), arterial hypertension, arterial fibrillation and valve diseases have therefore been studied. To search for sources and analyses of existing data on these conditions, we collaborated with the Scientific Section of the SEC, which provided records and studies on various diseases in Spain last year. We would like to thank, above all, the Sections of Ischemic and Coronary Units; Cardiac Insufficiency, Heart Transplantation and other therapeutic alternatives; Arterial Hypertension; Cardiology and Outpatient Clinic and Electrophysiology and Arrhythmia, for providing records and studies and performing an in-depth analysis of gender using existing data. We have also received the participation of the Working Group of Cardiovascular Disease in Women, whose Board of Directors we would also like to thank for their cooperation. Equally, the Working Group of Cardiac Insufficiency of the Andalusia Society of Cardiology provided records on this subject. Finally, we wish to thank the sponsorship and collaboration of the Centre of the Health of Women of the Ministry of Health, personified by its director, Concepción Colomer.

The results of these two years of work are presented in this supplement to the *Spanish Journal of Cardiology*. These results, presented below in articles on the various diseases studied, clearly demonstrate that there are significant differences in the characteristics of cardiovascular disease among men and women. There are also differences, which are

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consistently unfavourable to women, in diagnostic and therapeutic handling, especially for acute coronary syndrome and heart failure, which are conditions with increased severity and worse prognosis.

Another conclusion we can highlight is that there is insufficient evidence on two important problems: atrial fibrillation and valve disease. Therefore, it appears that designing studies specifically aimed at resolving these unanswered questions is necessary.

We hope that the results of this study, clearly presented by the authors of each article (whom we appreciate for their dedication to the project and

rigorous analysis), contribute to a greater knowledge of the reality of the gender influence on cardiovascular disease in Spain and better cardiac care for women suffering from these diseases in our country.

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Abbreviations

ASA: acetylsalicylic acid.	HT: hypertension.
PTCA: percutaneous transluminal coronary angioplasty.	LVH: left ventricular hypertrophy.
LCA: stroke.	AMI: acute myocardial infarction.
ARA-II: Angiotensin II receptor antagonists.	ACE INHIBITORS: angiotensin converting enzyme inhibitors.
AVB: atrioventricular blocking.	BMI: body mass index.
CVS: cardiovascular surgery.	NIS: National Institute of Statistics.
IHD: ischemic heart disease.	AAI: arm-ankle index.
IAD: implantable automatic defibrillator.	DCM: dilated cardiomyopathy.
DM: diabetes mellitus.	OR: odds ratio.
IDDM: insulin dependent diabetes mellitus.	BP: blood pressure.
CVD: cardiovascular disease.	PVR: pulmonary vascular resistance.
COPD: chronic obstructive pulmonary disease.	ACS: acute coronary syndrome.
VGD: vascular graft disease.	ACSWSTE: acute coronary syndrome with the ST elevation.
AF: atrial fibrillation.	ACSWOSTE: acute coronary syndrome without the ST elevation.
AGF: acute graft failure.	SCS: Spanish Cardiology Society.
LVFE: left ventricular fraction ejection.	MS: metabolic syndrome.
CVRF: cardiovascular risk factors.	
GP: glycoprotein.	

Methodology Employed in the Study of Cardiovascular Disease in Women in Spain

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Cardiovascular disease is the leading cause of death in both men and women in countries like Spain. Nevertheless, the risk of cardiovascular disease in women is frequently underestimated because of the perception that women are «protected» against ischemic heart disease. Moreover, the clinical manifestations of coronary disease in women can differ from those observed in men. These two factors can lead to poorer care in women with any type of cardiovascular disease, not only coronary disease, and to a worse prognosis. This article reviews some features of the sex differences observed in cardiovascular risk factors for, and in the clinical characteristics, treatment and prognosis of, cardiovascular disease. In addition, the general methodological approach employed in a current study of cardiovascular disease in women in Spain is described.

Key words: *Cardiovascular disease. Sex differences. Ischemic heart disease.*

Diseño general del proyecto de estudio sobre la situación de la enfermedad cardiovascular de la mujer en España

Las enfermedades cardiovasculares son la causa principal de mortalidad de varones y mujeres en los países de nuestro entorno. Sin embargo, el riesgo de la enfermedad cardiovascular en la mujer se subestima frecuentemente, debido a la percepción de que las mujeres están «protegidas» contra la cardiopatía isquémica. Además, las manifestaciones clínicas de la enfermedad coronaria en las mujeres pueden ser distintas de las observadas en los varones. Estos factores pueden llevar a una peor atención a las mujeres que sufren enfermedades cardiovasculares, no sólo cardiopatía isquémica, y a un peor pronóstico. En este artículo se discuten algunos aspectos relacionados con las diferencias en los factores de riesgo cardiovascular, las características clínicas, el tratamiento y el pronóstico relacionados con el sexo, y se detalla la metodología general del proyecto de estudio sobre la situación en España de la enfermedad cardiovascular en la mujer.

Palabras clave: *Enfermedad cardiovascular. Diferencias de sexo. Cardiopatía isquémica.*

BACKGROUND AND JUSTIFICATION

In Spain, as in other parts of the Western world, cardiovascular disease is the leading cause of death in women. In Europe, one woman dies every 6 minutes from the disease. In contrast, one woman dies every

minute from cardiovascular disease in the US¹⁻³. Despite the gravity of these data, women themselves still consider this a “man’s disease”. Fortunately, recent years have brought a change in this sentiment in part because of the attention devoted to the matter by health professionals and scientific societies, such as the Sociedad Europea de Cardiología (in English, the European Society of Cardiology), the American Heart Association, and others. Such societies have ongoing clinical and social education programs that will no doubt continue to increase understanding of this public health concern and foster positive changes in the public’s attitude toward cardiovascular disease. A significant advance has been the publication of

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cardiovascular disease prevention literature targeted at female readers.

Over the last 20 years, enormous effort has been invested in cardiovascular research and, specifically, at heart attack prevention, which has resulted in exciting and encouraging findings. Although these efforts have led to significant decreases in ischemic mortality overall, women have not benefited to the same degree as men have.

Heart attack risk factors vary between gender, a fact that has been repeatedly demonstrated by studies looking at cardiac risk factors, clinical manifestations, results of diagnostic tests, and application of therapeutic measures. In addition, the prognosis for female patients is worse than for men, in part because they tend to be older, have more co-morbidities, are diagnosed at later stages, and tend to infrequently receive some treatments⁴⁻¹¹.

We must not forget that the majority of medical action is based on studies with predominantly male participants. Until a few years ago, databases maintained by research institutes and clinical trials were largely devoid of female participants. For example, well accepted therapeutic interventions, such as the use of statins to prevent primary and secondary heart attacks, are based on clinical trials composed of fewer than 20% female patients, and the bulk of the information about the management of cardiovascular disease in women derives from studies where females make up less than 30% of the population being analysed. As a result, studies designed with women in mind are essential, whether it be through adequate enrolment of women in larger trials or by undertaking studies exclusively of the female population.

Recently, in the United States, the National Heart, Lung and Blood Institute has initiated an ambitious study of ischemic heart disease in women known as WISE (Women's Ischemic Syndrome Evaluation)¹², with the three-fold aim of optimising clinical evaluation and diagnostic testing for coronary disease, investigating the mechanism of myocardial ischemia in the absence of coronary stenosis, and evaluating the influence of hormones in the clinic and on the results of diagnostic testing. Regardless of the results obtained from the study, some general recommendations and objectives were issued:

1. Improve the understanding of the pathology and pathophysiology of the differences in heart attack: metabolic syndrome, physiology of reproductive hormones, role of the endothelium, genetic factors, proteomics, the hormone cycle, pain threshold, environmental and psychosocial factors.

2. Improve the understanding of symptoms and diagnostic tools including understanding the diverse manifestations of chest pains associated with coronary

illness caused by obstruction or lack of obstruction, the development and validation of better diagnostic methods for the detection of ischemia, and the development of studies to evaluate prodromes in patients without acute coronary syndrome.

3. Promote clinical investigation specific to females (basic data, clinical studies designed to evaluate diagnostics tests and their differences, natural history, treatment, and evolution). It is necessary that new studies be stratified by gender.

4. Investigate the mechanisms leading to adverse cardiovascular events during the early phase of hormone therapy: genetic and pharmacological factors, alternative formulations of hormone therapy and effects of estrogens.

5. Promote the translation of research into clinical practice: stimulate research and its clinical application to more effectively influence the education of the community as well as scientific enterprise.

Recently, the following noteworthy data were released from the WISE study:

– Role of hormones: The elevated concentrations of oestrogens before menopause and the reduced oestrogen and progesterone levels after menopause influence the risk of heart attack in women. In younger women, it appears that oestrogen deficiency caused by dysfunction of the ovaries is an important risk factor. In addition, women that experience an interruption in ovulation, and consequently the reduced production of oestrogens, are at higher risk for coronary disease.

– Diagnostic tests: The use of isotope studies is recommended. Single Photon Emission Computed Tomography (SPECT) has greatly improved diagnostic efficiency.

– Prognostics: Functional capacity is a powerful and consistent prognostic indicator. Since it is not feasible to carry out conventional strength tests in all women, practitioners should consider pharmacological stress tests. In addition, questionnaires, such as the Duke Activity Status Index (DASI), that evaluate daily activities offer valuable prognostic information. The results can be expressed in METs, and a clear relationship has been observed with clinical events.

– Obesity: Overweight women are at higher risk of coronary disease compared to women of normal weight, not simply due to the added weight but also to the metabolic alterations that accompany the condition.

– Specific factors: the possibility that other pathophysiological factors, such as inflammation, anaemia, or dysfunction of the microvasculature, affect the risk of heart attack in women has brought about the development of new diagnostic and prognostic tools. Examples include C-reactive protein and haemoglobin levels and the evaluation of arterial

narrowing in the retinas or the detection of coronary calcifications.

In our country, different scientific sectors of the Sociedad Española de Cardiología (Spanish Cardiology Society) have promoted the formation of databases to collect information on different aspects of cardiovascular disease, from which could be extracted female-specific information. However, to date, no studies exist that are dedicated solely to the female population. In recent years, ample information has been generated regarding cardiovascular atherosclerosis disease in females, comprising initial aspects of the disease, such as the presence and specifics of risk factors up to the most advanced diagnostic methods and therapeutics in other cardiology fields. Even though clear differences exist [between genders]; these have not been studied sufficiently. We make use of general data on factors such as cardiac insufficiency, arrhythmias, valve irregularities, and cardiomyopathies, but there are, as yet, no registries addressing these pathologies in a way that allows us to understand if there are specific characteristics of females that influence the disease progression.

The improved understanding of all implicating factors would provide not only the base for better diagnostics and treatment but also the development of preventative recommendations, such as has occurred with the publication of the cardiovascular disease prevention guides for women by 12 scientific societies, including the American Heart Association, the American College of Cardiology, the American Women Medical Association and the World Heart Federation. These guides were also accepted by 22 other institutions. In these guides, coronary disease is the main subject, but other health concerns that impact women, such as atrial fibrillation and the prevention of stroke, are also discussed¹³⁻¹⁶.

Fortunately, a greater sensitivity has developed among some classes of health care workers regarding these problems in recent years, but the concern must extend to the general population, to all health care professionals, scientific institutions, and ultimately to the government¹⁷. It is our collective responsibility to reduce the dramatic consequences of cardiovascular disease in females. A project, such as the one presented herein, that is capable of providing real information about the status of cardiovascular disease in Spain and the alleged gender discrepancies will be a major step forward in this direction.

OBJECTIVE

The overarching objective of this study is to ascertain the current status of cardiovascular disease in Spanish women, including an analysis of the current

treatment modalities and the cardiovascular disease characteristics most relevant to the women in our country. The end goal of the study is to determine if there are differences compared to males and to recommend strategies to improve the discrepancies and negative aspects that are uncovered.

GENERAL DESIGN OF THE PROJECT

This project is an initiative of the Agencia de Investigación de la Sociedad Española de Cardiología, or SEC, (Research Agency of the Spanish Society of Cardiology) with the participation of all its scientific sectors. It consists of 4 phases:

1. Design of the protocol and project methodology.
2. Analysis of data from SEC studies carried out in recent years.
3. Formulation of the final report and specific recommendations.
4. Dissemination of the results.

The general protocol was drawn up in the first half of 2006. The second phase (analysis of the database and available studies) took place in the second half of 2006 and in the first trimester of 2007. The final analysis of the data occurred in the second and third trimester of 2007, after which the final report was compiled; recommendations for the future were made and are included elsewhere in this document. Once the suggestions of the scientific sectors of the SEC were analysed, the study focused on the most common cardiovascular illnesses because of their higher prevalence and their prognostic importance. These included ischemic cardiomyopathy (acute coronary syndrome), arterial hypertension, cardiac insufficiency, atrial fibrillation, and valve pathologies. Specific problems have also been analysed that exist in the source data from the SEC registries (for example, heart transplants). In each of these cases, specific objectives have been singled out for response. The general methodology of the second phase of the study is to perform a comparative analysis by gender (females to males) using the existing databases, which will be carried out by the different sectors of the SEC. These databases are rich in data and can potentially answer the majority of questions about these fields. We have also attempted to identify which illnesses are not adequately represented in the source data.

SPECIFIC AIMS

The specific aims vary somewhat according to the specific disease state, but the aim is essentially to attempt to answer whether there are differences between men and women in clinical characteristics and risk factors of each disease, in the implementation

TABLE 1. Specific aims of the project focused on cardiovascular disease in the female population

Demographics and risk factors
Diagnostic tests
Revascularisation following acute coronary syndromes
Secondary prevention measures (pharmacologic or non-pharmacologic)
Mortality
Cardiac insufficiency
Clinical characteristics
Aetiology
Diagnostic tests (determining ventricular function and myocardial ischemia)
Adequacy of pharmacological treatments
Heart transplant
Arterial hypertension
Left ventricular hypertrophy
Adequate control of hypertension
Pharmacological treatments
Concomitant cardiovascular diseases
Atrial fibrillation
Prevalence
Co-morbidities
Anticoagulants
Treatment modalities (cardiac-specific and control of frequency)
Complications (embolisms)
Valve pathologies
Aetiology
Clinical characteristics
Surgical treatments and their results

of diagnostic tests and in the treatment received (be it pharmacologic or not). In some cases, differences in morbidity and mortality will also be studied. Table 1 outlines the specific aims of the project.

CONCLUSION

This article summarises the methodology of a project focused on cardiovascular disease in the female population that is being carried out by the research arm of the SEC. Findings of the project are presented in subsequent works within this volume

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Influence of Sex on Acute Coronary Syndrome Mortality and Treatment in Spain

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Coronary heart disease is a major health problem in women. In Spain, it is the cause of death in 10%. The aim of this study was to investigate possible sex differences in the clinical characteristics, cardiovascular risk profile, diagnostic assessment, treatment and prognosis of patients admitted with acute coronary syndrome (ACS) in Spain between 1994–2002. Data from trials conducted by the Working Group on Ischemic Heart Disease and Coronary Care Units of the Spanish Society of Cardiology Section during this period (i.e., RISCO, PRIAMHO I and II, DESCARTES and TRIANA) were analyzed. Data were reclassified and combined into a single database that included 48,369 patients (75.7% male and 24.3% female). Of these, 13,405 (26.6% female) had non-ST-elevation acute coronary syndrome (NSTEMACS), while 34,334 (23.2% female) had ST-elevation acute coronary syndrome (STEMACS). Compared with men, women were older, had a worse cardiovascular risk profile, more often had a history of heart failure, received beta-blockers and statins less often, were less likely to undergo percutaneous revascularization, presented on admission with a 50% higher mortality rate and incidence of serious adverse events, and had higher mortality during follow-up. The sex differences in those with STEACS were similar: fewer women underwent coronary reperfusion and the time to reperfusion was significantly longer. In addition, the initial mortality, in-hospital complication and 1-month mortality rates in women were double those in men. However, female gender was an independent predictor of in-hospital, 1-month and 1-year mortality only for STEACS, and not for NSTEMACS. In conclusion, sex differences were found in the clinical profile and management of patients admitted for ACS. However, sex was an independent predictor of mortality only in those with STEACS.

Key words: *Acute coronary syndrome. Sex differences. Prognosis*

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Influencia del sexo en la mortalidad y el manejo del síndrome coronario agudo en España

La cardiopatía isquémica es un problema relevante de salud en la mujer. Supone en España la causa de muerte del 10% de las mujeres. El objetivo de este estudio es analizar las posibles diferencias por sexo en las características clínicas, el perfil de riesgo cardiovascular, las medidas diagnósticas, el tratamiento y el pronóstico de los pacientes ingresados con síndromes coronarios agudos (SCA) en España de 1994 a 2002. Para ello se han analizado los resultados de los registros de la Sección de Cardiopatía Isquémica y Unidades Coronarias de la Sociedad Española de Cardiología realizados en ese período (RISCO, PRIAMHO I y II, DESCARTES y TRIANA). Se efectuó una recodificación de las variables y la fusión en una única base de datos, de lo que resultó una muestra de 48.369 pacientes (el 75,7% varones y el 24,3% mujeres). En 13.405 pacientes se trataba de un SCASEST (el 26,6% de mujeres) y en 34.334 casos, de un SCACEST (el 23,2% de mujeres). Las mujeres tenían, respecto a los varones, una edad superior, un perfil de riesgo cardiovascular más desfavorable y antecedentes más frecuentes de insuficiencia cardíaca, recibieron con menor frecuencia bloqueadores beta y estatinas, se sometieron a intervencionismo coronario en menor proporción y presentaron mortalidad e incidencia de eventos adversos graves durante el ingreso un 50% superiores a las de los varones y mayor mortalidad en el seguimiento. Los resultados en el SCACEST presentaron las mismas diferencias en relación con el sexo; el porcentaje de mujeres sometidas a reperusión fue inferior al de varones y el tiempo hasta la reperusión, significativamente mayor en las mujeres. La mortalidad y las complicaciones hospitalarias y la mortalidad al mes en las mujeres duplicaron las de los varones. Sin embargo, el sexo femenino fue un predictor independiente de mortalidad hospitalaria a 1 mes y a 1 año en el SCACEST, pero no en el SCASEST. En conclusión, el estudio detecta diferencias en el perfil clínico y en el manejo relacionadas con el sexo de los pacientes ingresados por SCA en el período estudiado, aunque sólo el sexo se mostró como predictor independiente de mortalidad en el SCACEST.

Palabras clave: *Síndrome coronario agudo. Diferencias por sexo. Pronóstico.*

INTRODUCTION

Cardiovascular disease (CVD) constitutes the leading cause of death for women in developed countries. It is a more common cause of death than cancer and leads to one death every minute. At present, the number of female deaths due to CVD in the United States exceeds that of men. Additionally, its impact on overall mortality rates in Europe is greater for women than it is for men, where coronary artery disease is the main cause of these deaths¹⁻³. In Spain, according to data from the National Statistics Institute (NSI) that were taken from the document “Estrategia de Cardiopatía Isquémica del Sistema Nacional de Salud” (Strategy for Ischaemic Heart Disease of the National Health System) that was published by the Ministry of Health and Consumption⁴, CVD is the number one cause of death in the Spanish population. The gross mortality rate is 315/100,000 inhabitants, which is equal to 35% of all deaths in Spain (data from NSI, 2003). Among the different cardiovascular diseases that comprise CVD, ischaemic heart disease causes the greatest number of deaths of cardiovascular origin (31% of the total; 40% of the total for men and 24% of the total for women)⁵. These data mean that ischaemic heart disease is the cause of death for 12% of men and for 10% of women among Spaniards. Additionally, this report indicates that the associated morbidity rate is 352/100,000 inhabitants (493/100,000 for men and 215/100,000 for women). Regarding trends in the prevalence of CVD, the existing data show that the incidence of acute myocardial infarction (AMI) remains stable. However, estimates based on this data postulate the number of patients with AMI and angina pectoris who will be admitted to Spanish hospitals will increase by 1.5% annually due to the aging of the population. This means that each year, the number of people checking into hospitals for the treatment of AMI or angina pectoris will increase by 2,000. On the other hand, advances in the management and treatment of acute coronary syndrome (ACS) have translated into a decrease in mortality rates. Two factors, the increase in the median age of the population and the decrease in ACS-related mortality, have led to an increase in the prevalence of ischaemic heart disease as well as an increase in associated morbidity rates. Therefore, it is expected that ischaemic heart disease will continue to require the allotment of a large and progressively increasing number of resources.

The same report⁴ from the Ministry of Health and Consumption emphasises that the mortality rate of patients with AMI is greater among women than among men, independent of age. In a recent publication that analysed the epidemiology of CVD in women⁵, it was shown that the 28-day mortality rate after a first AMI is 20% greater in women after adjusting for patient age, especially in countries like Spain that have a relatively

low incidence of ischaemic heart disease. A lower intensity of treatment has been observed among women as compared to men. Fewer invasive studies are performed in women than in men and women tend to be underdiagnosed and undertreated as compared to men. In addition, more specific studies are needed to demonstrate the benefit of various therapeutic strategies in women, since it is clear that have been underrepresented in previous clinical studies^{5,6}. Ischaemic heart disease in women seems to have unique characteristics that have not yet been well elucidated. As Heras⁶ has indicated, “in spite of the importance of the health problems caused by ischaemic heart disease in women, knowledge of the specific characteristics of its clinical presentation, treatment, and prognosis are little studied, due in large part to the insufficient presence of women in clinical studies.”

All of the issues mentioned above underscore the relevance of studies that continue to deepen the knowledge of the differences in the presentation, development, and treatment of ACS between men and women in Spain in order to improve the management of ischaemic heart disease in women. The Ischaemic Heart Disease Section and Coronary Units of the Spanish Society of Cardiology as well as the “Cardiovascular Disease in Women, a Study of the Situation in Spain” study that has been promoted by the Research Agency of the Spanish Cardiology Society, encouraged us to undertake this study. The objective of the study was to increase the amount of information available in the literature regarding the influence of gender on the clinical characteristics, management, and associated mortality rates of ACS in Spain. The concrete objective of the study was to examine the: a) demographic characteristics; b) risk profiles; c) clinical presentations; d) medium-term (1 month) clinical outcomes, and e) utilisation of resources to identify gender-related differences among Spanish men and women with ACS. The ultimate goal of this analysis was to identify ways to improve the management of women with ACS as well as to propose specific interventions that may lead to better outcomes among women with ACS.

METHODS

Source of information—records of the Ischaemic Heart Disease Section and Coronary Units of the Spanish Cardiology Society

In order to examine gender-related differences among patients with ACS, we examined the results of various tests that had been performed on patients with ACS. To do so, we examined the hospital records of patients with ACS that were collected over the course

of the previous decade by the Ischaemic Heart Disease Section and Coronary Unit of the Spanish Cardiology Society. The studies to which this paper refers are RISC⁷, PRIAMHO I^{8,9} and II¹⁰, DESCARTE¹¹, and TRIANA^{12,13}. Patients whose records were available for review and who were seen between 1994 and 2002 were considered for inclusion in this study. Information regarding the various studies that were assessed in this analysis are summarised below:

– The RISC⁷ study (Spanish acronym for Registry of Infarctions of the Ischaemic Heart Disease Section and Coronary Unit)⁷: In this registry, the majority of hospitals that have a coronary unit (47 hospitals) were invited to participate and between 27 and 32 hospitals participated each year. Information was collected from patients who were admitted to the coronary unit with AMI between 1995 and 1999. A total of 28,537 patients were registered, of which at least 25% were women. Information was collected regarding the characteristics of included patients, the treatments they received, and their course in the coronary unit.

– The PRIAMHO I study (Spanish acronym for Registry Project for Acute Myocardial Infarction in Hospitals)^{8,9}: This is a voluntary registry in which the coronary units of hospital centres of Spain were invited to participate. A total of 24 hospitals that met rigorous selection criteria participated in the study, which included 5,242 patients who were admitted to coronary units in the participating hospitals with AMI between October 1994 and September 1995. The registry contains information on the demographic characteristics, clinical characteristics, management, and clinical course (over a one-year follow-up period) of the included patients. In this study, 22.6% of the patients included in the registry were women.

– The PRIAMHO II study (Spanish acronym for Registry Project for Acute Myocardial Infarction in Hospitals)¹⁰: A total of 58 hospitals of the 81 hospitals that were randomly selected from a pool of 165 hospitals that could care for patients with AMI and met the study's criteria participated in the study. A total of 6,221 patients with AMI were admitted to the participating hospitals between the May 15th and December 15th of 2000. Of these, 25% were women. This study presented information on the demographic characteristics, clinical characteristics, management, and clinical course (over a one-year follow-up period) of the included patients.

– The DESCARTE¹¹ study (Spanish acronym for Description of the State of Acute Coronary Syndromes in a Temporary Spanish Registry)¹¹: This registry collected information from patients with a diagnosis of acute coronary syndrome without ST elevation who were admitted to one of 53 participating Spanish hospitals between April and May of 2002. The study included 1,877 patients, of which 33.7% were women.

This study presented information on the demographic characteristics, clinical characteristics, management, and clinical course (over a one-year follow-up period) of the included patients.

– The TRIANA Registry^{12,13}: This was a prospective, multi-centre study in which all Spanish medical centres that performed a minimum of 50 angioplasties per year were invited to participate. This study was jointly performed by the Ischaemic Heart Disease Section and Cardiac Unit and the Hemodynamic and Interventional Cardiology Section of the Spanish Society of Cardiology. In total, 26 centres accepted the invitation to participate. In TRIANA 2, all patients >75 years of age who were admitted to participating hospitals between March 18th and July 31st of 2002 for AMI with ST segment elevation or with a complete left bundle branch block who did not receive primary angioplasty or rescue were included in the study. In the TRIANA 1 registry, 459 patients were included over a similar time period, but the recruitment period was one month shorter than it was in TRIANA 2. The TRIANA 1 and TRIANA 2 registries included information on more than 520 patients with AMI and ST segment elevation who were treated in a coronary unit or on the floor in plant during 2002.

All of the patients who were included in the aforementioned registries were included in this study.

Recodification of variables and creation of unique database

In order to assess all of the patients who were included in the aforementioned registries, the variables from each registry had to be recoded so that a joint database could be created. All were designed and performed by the Ischaemic Heart Disease Section and Coronary Unit of the Spanish Society of Cardiology. Subsequently, the analysis and evaluation was jointly carried out. Although there were differences in the type of information that was available in the registries, the clinical variables that were available in all of the registries were selected for further study. The clinical variables that are listed in the following section were able to be extracted from all of the registries:

– Demographic characteristics and risk factors: age, gender, diabetes, tobacco use, dyslipidaemia, and arterial hypertension.

– Prior cardiovascular events: previous infarction, angina, revascularisation, cerebrovascular accident (CVA), claudication, and congestive cardiac failure.

– Time: time elapsed from the onset of symptoms#fderechahospitalisation and time elapsed from the onset of symptoms#fderechareperfusion (< 6 hours, 6 to 12 hours, > 12 hours) for patients with acute coronary syndrome with ST-elevation.

TABLE 1. The number and gender of patients included in the acute coronary syndrome registries associated with the Ischaemic Heart Disease Section and Coronary Unit of the Spanish Society of Cardiology and the total unified database

	Men, n (%)	Women, n (%)	Total, n
DESCARTES	1,245 (66.3)	632 (33.7)	1,877
PRIAMHO I	4,058 (77.4)	1,184 (22.6)	5,242
PRIAMHO II	4,648 (74.7)	1,571 (25.3)	6,219
TRIANA 1	373 (81.3)	86 (18.7)	459
TRIANA 2	148 (48.2)	159 (51.8)	307
RISCI	26,121 (76.2)	8,144 (23.8)	34,265
Total	36,593 (75.7)	11,776 (24.3)	48,369

– Characteristics measured at the time of admission: vital signs (such as blood pressure and heart rate), Killip classification, electrocardiographic localisation of the AMI (anterior, posterior, other), electrocardiographic presentation.

– Hospital treatments: fibrinolysis or primary angioplasty, as well as treatment with antiplatelet agents, acetylsalicylic acid, clopidogrel, unfractionated heparin, low molecular weight heparin, glycoprotein IIb/IIIa inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), statins, digoxin, diuretics, and inotropes.

– Procedures performed during hospitalisation: echocardiogram, ergometry, stress echocardiography, isotopic evidence detection of ischaemia, coronary angiography, coronary angioplasty, coronary surgery, left ventricular ejection fraction (LVEF)² (classified as $\leq 40\%$ or $> 40\%$), and evaluation of the number of vessels with significant lesions.

– Hospital course: hospital death, AMI/acute myocardial reinfarction, recurrent angina/post-AMI angina, maximum Killip classification, cardiogenic shock, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, advanced atrioventricular block (AVB), haemorrhage, CVA, and type of CVA (if one did occur).

– Discharge medications: acetylsalicylic acid, clopidogrel, ticlopidine, trifusal, beta-blockers, ACEI, statins, nitrates, and calcium channel blockers.

– Follow up: until death or after 28 days after discharge.

By merging the six databases, we created a single database with 48,369 patients, of whom 36,593 (75.7%) were male and 11,776 (24.3%) were female. Table 1 shows the number and gender of patients in the final merged database and in each of the registries from which the database was constructed. Subsequently, given the differences in the disease processes themselves, four groups were created: a) patients with unstable angina (n = 976); b) patients

TABLE 2. Proportion of men and women in the study populations

	Men, n (%)	Women, n (%)	Total
Population 1: unstable angina	666 (68.2)	310 (31.8)	976
Population 2: Non-Q-wave AMI	9,173 (73.8)	3,256 (26.2)	12,429
Population 3: NSTEMI-ACS	9,839 (73.4)	3,566 (26.6)	13,405
Population 4: STE-ACS	26,380 (76.8)	7,954 (23.2)	34,334

AMI: acute myocardial infarction; NSTEMI-ACS: non ST-elevation acute coronary syndrome; STE-ACS: ST-elevation acute coronary syndrome.

with non-Q-wave AMI (n = 12,429); c) patients with unstable angina or with non-Q-wave AMI (NSTEMI-ACS), that is, the sum of the first two groups (a and b) (n = 13,405); and d) patients with AMI with ST-segment elevation (STE-ACS) (n = 34,344) (table 2). Groups c and d were analysed separately to evaluate the objectives of the study, which were to identify gender-related differences between ACS patients as well as to examine the clinical characteristics, the cardiovascular risk profiles, the diagnostic measures that were taken, the treatments that were given, and the prognosis of the patients that were included in the study and had NSTEMI-ACS or STE-ACS.

Criteria used to assign patients in the NSTEMI-ACS and STE-ACS groups

To assign patients to the NSTEMI-ACS and STE-ACS groups, the diagnosis the patient was given at the time of admission was used, since the discharge diagnosis was not available in any of the registries with the exception of the DESCARTES study. All of the patients from the DESCARTES database were considered to have NSTEMI-ACS, but 331 patients were ultimately excluded because the aetiology of their symptoms were deemed not to be due to ACS and it was not listed as a discharge diagnosis. Patients in the other registries had to have a diagnosis of myocardial infarction to be included in the registry. Patients from the PRIAMHO I-II and RISCI databases were considered to have had NSTEMI-ACS if they presented to the coronary unit with a non-Q-wave AMI and were considered to have had STE-ACS if they presented to the coronary unit with Q-wave AMI. All of the patients from the TRIANA 1-2 databases were classified as having had STE-ACS due to the inclusion criteria of the registry.

Statistical analysis

The available characteristics of patients in groups c and d were compared by gender, including patients' baseline characteristics and hospital course as well as their short-term and long-term rates. All analyses were using the SPSS statistical software package, version 14.0. The categorical variables were compared using

TABLE 3. Sociodemographic and clinical characteristics of the study population, stratified by type of ACS (NTSE-ACS vs. STE-ACS)

	Men	Women	Total	p
NSTE-ACS group				
Age (years), mean \pm SD	64.9 \pm 12	70.9 \pm 10.5	66.5 \pm 11.9	< 0.001
Patients, n (%)	9,839 (73.4)	3,566 (26.1)	13,405 (100)	
Cardiovascular risk factors, n (%)				
Hypertension	4,610 (46.9)	2,401 (67.4)	7,011 (52.4)	< 0.001
Diabetes mellitus	2,540 (25.8)	1,472 (41.3)	4,012 (30)	< 0.001
Dyslipidaemia	3,680 (37.5)	1,406 (39.6)	5,086 (38)	0.029
Tobacco use	5,475 (55.8)	318 (8.9)	5,793 (43.3)	< 0.001
Previous cardiovascular events, n (%)				
Myocardial infarction	2,865 (29.2)	822 (23.1)	3,678 (27.5)	< 0.001
Angina	886 (44.4)	380 (47.6)	1,266 (45.3)	NS
Revascularisation	646 (8.3)	155 (5.6)	801 (7.6)	< 0.001
Stroke	99 (9.6)	38 (8)	137 (9.1)	NS
Claudication	237 (11.9)	41 (5.1)	278 (10)	< 0.001
Heart failure	83 (8.1)	80 (16.8)	163 (10.8)	< 0.001
STE-ACS group				
Age (years), mean \pm SD	62.6 \pm 12.5	71.4 \pm 11.1	64.7 \pm 12.7	< 0.001
Patients, n (%)	26,380 (76.8)	7,954 (23.2)	34,334 (100)	
Cardiovascular risk factors, n (%)				
Hypertension	10,029 (38)	4,785 (60.2)	14,814 (43.2)	< 0.001
Diabetes mellitus	5,350 (20.3)	3,050 (38.4)	8,400 (24.5)	< 0.001
Dyslipidaemia	8,867 (33)	2,605 (32.9)	11,292 (32.9)	NS
Tobacco use	17,719 (67.3)	967 (12.2)	18,686 (54.5)	< 0.001
Previous cardiovascular events, n (%)				
Myocardial infarction	3,789 (14.4)	951 (12)	4,740 (13.8)	< 0.001
Angina	780 (22.5)	268 (25.7)	1,048 (23.2)	0.033
Revascularisation	779 (3.4)	193 (2.8)	972 (3.3)	0.014
Stroke	53 (10.2)	24 (10)	77 (10.1)	NS
Claudication	263 (7.6)	38 (3.7)	301 (6.7)	< 0.001
Heart failure	19 (3.7)	20 (8.3)	39 (5.1)	0.012

NS: no statistically significant differences; NSTE-ACS: non ST-elevation acute coronary syndrome; SD: standard deviation; STE-ACS: ST-elevation acute coronary syndrome.

the χ^2 test², while the continuous variables were compared via ANOVA. The threshold of significance for this study was $p = 0.05$. In addition, in order to identify the factors associated with in-hospital mortality and 28-day mortality, a binary regression analysis was performed. In addition to gender, the regression model included the clinical variables that were postulated to be potentially related to mortality, including age, arterial hypertension, diabetes, tobacco use, previous AMI, treatment with beta-blockers or with ACEIs, coronary angiography, delayed admission, and the type of reperfusion that was performed (no reperfusion, fibrinolysis or angioplasty).

RESULTS

Description of the study population

The sociodemographic and clinical characteristics of the study population are summarised in table 3. Men comprised 75% of the group of patients with STE-ACS. The mean age \pm the standard deviation (SD) of

the patients was 66.5 ± 11.9 , although it was observed that the women were, on average, 6 years older than the men, a finding that reached statistical significant significance. The mean age of the sample and the gender-related differences in age probably explain the statistically significant differences that were observed in terms of the presence of cardiovascular risk factors among women and men. For example, the women in the study were more likely to have hypertension, diabetes, or dyslipidaemia than the men in the study. Given that in this study, on average, the women were older than the men, it seems logical that there was a greater prevalence of these diseases among the women in this study. On the other hand, tobacco use was more prevalent in men and was in fact the only cardiovascular risk factor that was present in a greater percentage of men than women in this study. In fact, it is the risk factor for which the greatest differences were detected between groups of patients with regard to gender. The gender-related differences in rates of tobacco use, which were statistically significant, are very likely due to cultural factors.

TABLE 4. Hospital treatments and course, stratified by gender

	Men, n (%)	Women, n (%)	Total, n (%)	p
NSTE-ACS group				
Hospital treatments				
Antiplatelet agents	5,589 (89.2)	1,949 (88.2)	7,538 (88.9)	NS
Hospital course				
Death	758 (7.7)	409 (11.5)	1,167 (8.7)	< 0.001
Reinfarction	294 (3)	143 (4.1)	437 (3.3)	0.003
Post-AMI Angina	600 (6.8)	225 (7)	825 (6.9)	NS
Heart failure	1,565 (20.2)	827 (30.2)	2,392 (22.8)	< 0.001
Cardiogenic shock	552 (7.1)	286 (10.4)	838 (8)	< 0.001
NSTE-ACS group				
Hospital treatments				
Fibrinolysis	3,494 (53.6)	878 (43.6)	4,372 (51.3)	< 0.001
Primary angioplasty	741 (11.4)	193 (9.9)	934 (11.1)	NS
Antiplatelet agents	18,034 (90.8)	5,279 (89)	23,313 (90.4)	< 0.001
Acetylsalicylic acid	20,664 (97.6)	6,086 (97.1)	26,750 (97.5)	0.026
Hospital course				
Death	2,287 (8.7)	1,514 (19)	3,801 (11.1)	< 0.001
Reinfarction	760 (2.9)	391 (5)	1,151 (3.4)	< 0.001
Post-AMI Angina	525 (2.2)	200 (2.8)	725 (2.4)	0.006
Heart failure	4,374 (19)	929 (27.5)	6,303 (21)	< 0.001
Cardiogenic shock	1,785 (7.8)	1,163 (16.6)	2,948 (9.8)	< 0.001

AMI: acute myocardial infarction; NS: no statistically significant differences; NSTE-ACS: non ST-elevations acute coronary syndrome; STE-ACS: ST-elevation acute coronary syndrome.

In terms of the prior cardiac events that the patients in this study had experienced, angina was especially common among the NSTE-ACS patients: almost half of the study population had previously had an episode of angina. Additionally, 25% of the patients had had a myocardial infarction. When the incidence of CVA and angina were compared with regard to gender, there were hardly any differences between men and women. It was observed that a higher percentage of men had had a myocardial infarction (29.2%), claudication (11.9%), or revascularisation (8.3%) than women (23.1%, 5.1%, and 5.6%, respectively). All of these differences were statistically significant. In terms of prior history of congestive heart failure (CHF), 16.8% of the women had had a previous episode of CHF as compared to 8.1% of men. These differences were likely influenced by the fact that the women in this study were older and had a higher prevalence of hypertension than the men in the study.

The gender distribution of the patients who were diagnosed with STE-ACS was very similar to that of the group of patients with NSTE-ACS: 76.8% were men and 23.2% were women (table 3). In this group, women were an average of 8.8 years older than the men, a difference that was even more marked than in the NSTE-ACS group. There were also differences in the distribution of cardiovascular risk factors with regard to gender in this group. The predominant risk factor that was present among patients in this group was tobacco use: more than half of the included patients were smokers (54.5%). Hypertension and

diabetes were more frequent among the women in this group, while tobacco use was more frequent among the men. Statistically significant gender-related differences were not noted in terms with regard to the prevalence of dyslipidaemia. In terms of the prior history of cardiovascular events, it is worth emphasising that in this group, the percentage of patients that had had some sort of event was lower than in the NSTE-ACS group. Additionally, while there were gender-related differences in the prevalence of prior cardiac events, the differences were not as marked in this group as in the other groups. As with the NSTE-ACS group, the proportion of men with a history of myocardial infarction, claudication, or revascularisation in the STE-ACS group was greater than that of the women in the group. On the other hand, the women in this group were more likely to have previously suffered from angina (25.7%) or CHF (8.3%) than the men in the group (22.5% and 3.7%, respectively).

Treatment and hospital course

We analysed the information available regarding the hospital courses of the patients with ACS as well as the treatments they received during the course of their hospitalisation (table 4). For this analysis, patients with NSTE-ACS and with STE-ACS were divided into separate groups and we examined gender-related differences in the hospital courses and treatments within the two groups.

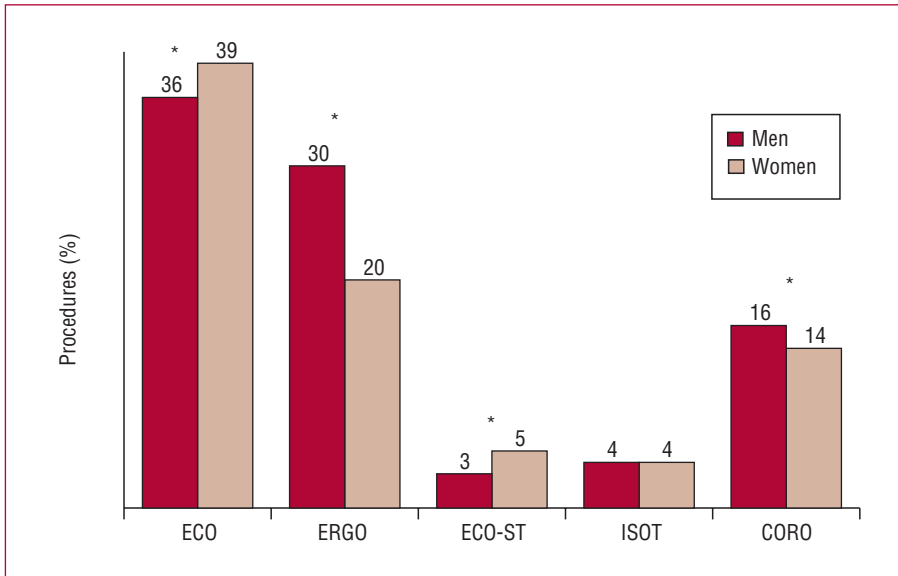


Fig. 1. Frequency with which diagnostic procedures were performed in men and women with NSTE-ACS. Information regarding the performance of coronary angiography (CORO) and echocardiography (ECO) was available for all patients, but was only available for 3,578 patients regarding ergometry (ERGO), stress echocardiography (ECO-ST), and isotope study (ISOT).

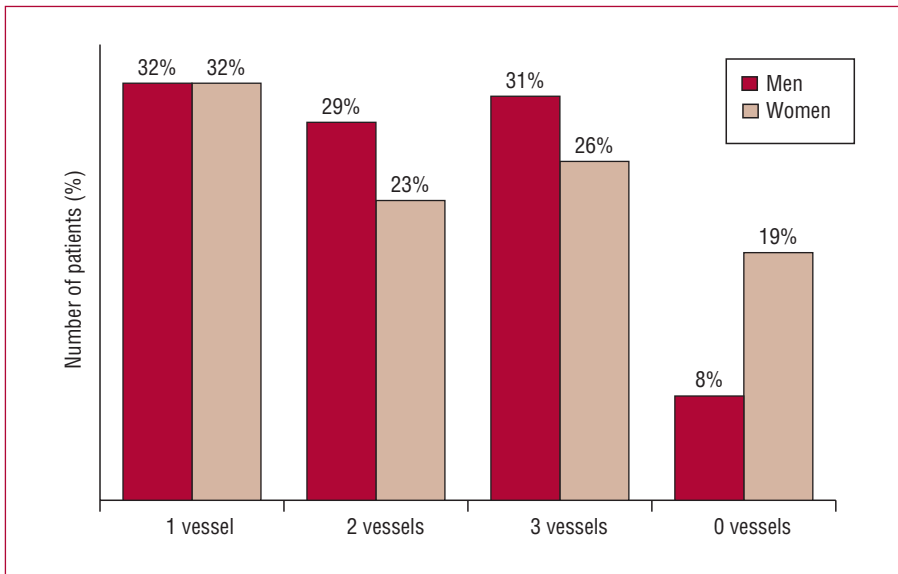


Fig. 2. Data on the extension of coronary disease in the group of men and women with acute coronary syndrome without ST segment elevation who underwent cardiac catheterism. This information was available for 681 patients.

NSTE-ACS Group

At the time of admission, acetylsalicylic acid and antiplatelet agents were the medications that were most often administered to patients (88% and 89%, respectively). There were no gender-related differences in the rate of medication administration except for with regard to the utilisation of beta-blockers and statins, which were administered more frequently in men than in women (44% vs. 41% and 63% vs. 56%, respectively) and of ACEI and diuretics, which were administered more frequently in women than in men (39% vs. 32% and 33% vs. 19%, respectively). Coronary angiography was performed less frequently in women than in men (fig. 1). The angiography findings of the women in the study

revealed that the women had a similar proportion of triple vessel disease than that of the men in the study, but were also less more likely to have angiographically normal coronary arteries (fig. 2). We also observed echocardiograms were more frequently and that stress tests were performed less frequently in the women in the study. These differences are largely explained by gender-related differences in age and previous or current history of heart failure. Overall, the intensity of treatment and the diagnostic efforts that were made during the course of the hospital course of these patients were lower among the women in this study.

In terms of the events that occurred during the patients' hospitalisation, the most frequent was among heart failure, which occurred in almost one fourth of

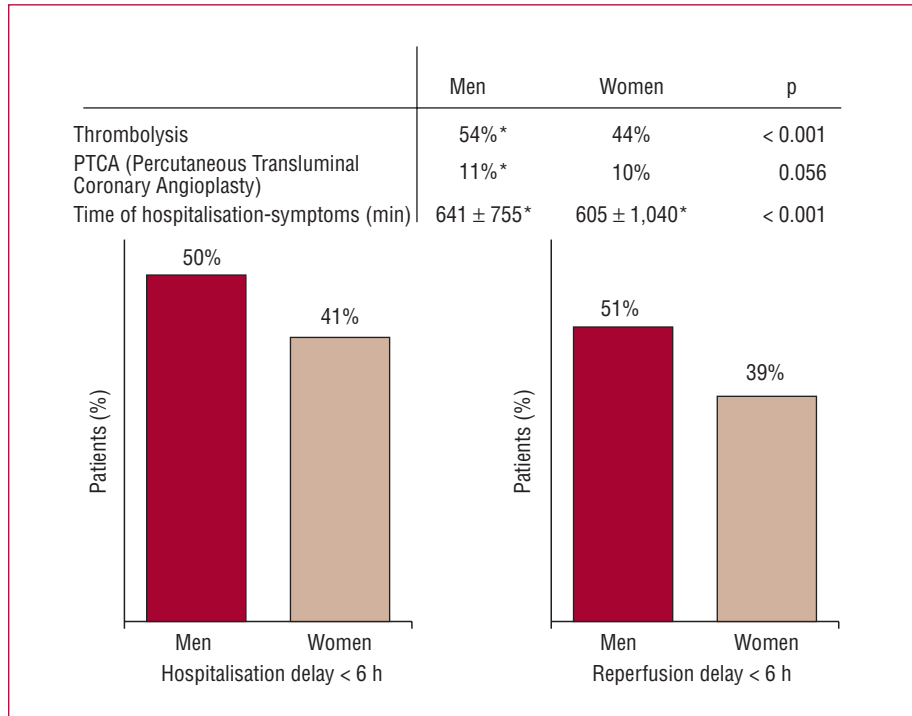


Fig. 3. Type of (information available for 6,516 patients) and delays in revascularisation (information available for 3,346 patients) among men and women with STE-ACS.

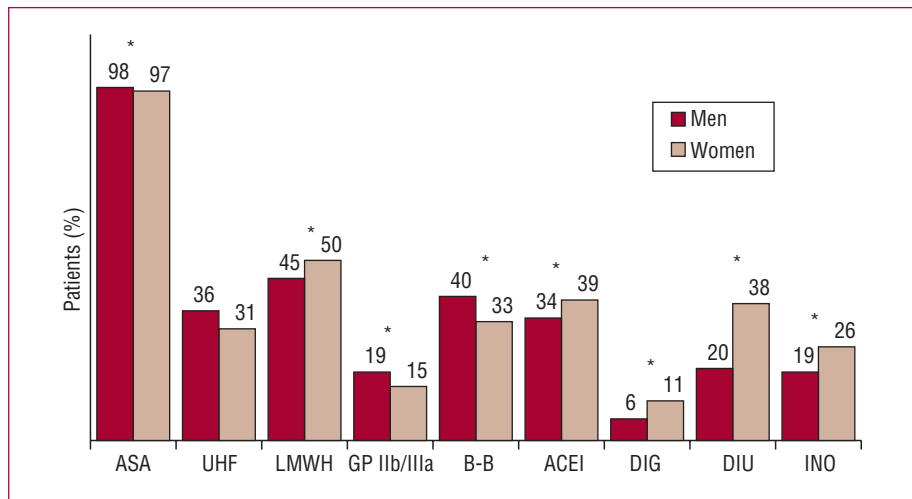


Fig. 4. Treatments utilised during the hospitalisation of women and men with STE-ACS.

the patients. All of the events that were assessed in the study (in-hospital death, reinfarction, post-infarction angina, heart failure, or cardiogenic shock) occurred more frequently among the women in this study than among the men. All of the gender-related differences, except for the rate of post-infarction angina, were statistically significant. As such, NSTEMI-ACS appears to be a more serious condition in women than it is in men.

STEMI-ACS group

The proportion of patients that received fibrinolysis exceeded 50%. There was a statistically significant

difference in the gender distribution of patients who received fibrinolysis, with men receiving the treatment more often than women (53% versus 43%). Differences were not noted with regard to the percentage of women and men that underwent primary angioplasty, with about 10% of both men and women undergoing the procedure (fig. 3). The time that elapsed between the onset of symptoms and reperfusion was greater for women than for men, both with regard to a delay between the onset of symptoms and initiation of medical care and with regard to the delay between hospital admission and the initiation of reperfusion.

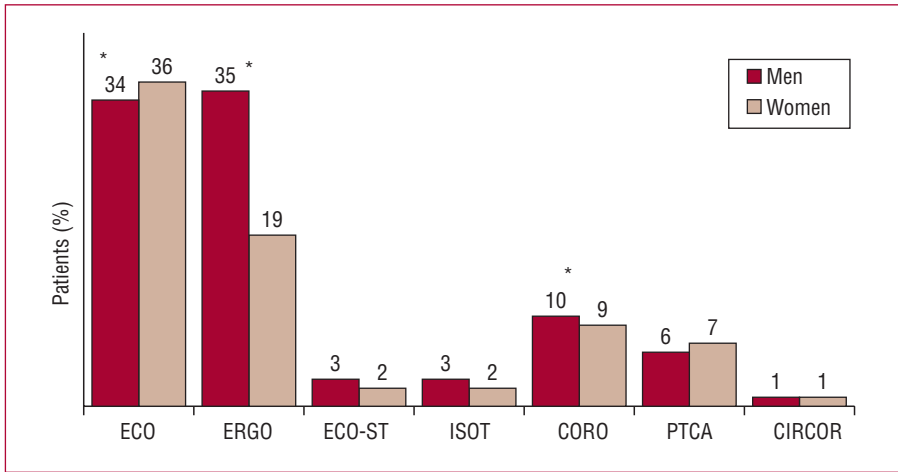


Fig. 5. Diagnostic and therapeutic procedures utilised during the hospitalisation of men and women with STE-ACS.

In terms of pharmacological treatment, the rate of utilisation of antiplatelet agents was high in both groups (> 90%). In spite of the fact that the aforementioned gender-related differences appeared to be relatively small, they were statistically significant due to the large number of patients that were included in this study. The utilisation of various pharmacological agents and diagnostic tests in this group was similar to that in the NSTEMI-ACS patient group. Women in this group were less likely to receive beta-blockers, glycoprotein IIb/IIIa inhibitors than the men in this group were and were less likely to undergo coronary angiography or stress tests. On the other hand, the rate of utilisation of ACEI, digoxin, diuretics, inotropes, and echocardiograms was greater among women than men in this group (figs. 4 and 5).

The hospital courses of the patients in this group were very similar to those of the patients in the NSTEMI-ACS group. The most frequent event that occurred during hospitalisation was CHF, which occurred in 20% of the patients in this group. Women were more likely to experience cardiac events during their hospital course than men were. For example, the percentage of women that died during their hospitalisation, had a myocardial infarction or reinfarction, or suffered from cardiogenic shock was

double that of the men in the group. All of these gender-related differences were statistically significant.

Mortality rates due to acute coronary syndrome

The in-hospital mortality and one-month mortality rates due to ACS were calculated for both the NSTEMI-ACS and the STE-ACS groups (table 5). In the NSTEMI-ACS group, the in-hospital mortality rate was high, at 8.7%. Women in this group had a 30% higher mortality rate than the men in this group (11.5% vs. 7.7%, respectively). In the group of patients with NSTEMI-ACS, the 28-day mortality rate was just over 9%. When men and women were examined separately, we found that the mortality rate of women was almost 4 percentage points higher and almost 50% higher than that of men (12.1% of females vs. 8.3% of males). This difference was statistically significant ($p < 0.001$) and very relevant clinically. The in-hospital mortality for the patients with STE-ACS was also high at 11.1%, much like it was in the NSTEMI-ACS group. Gender-related differences were also observed among patients in this group. The in-hospital mortality rate of women was more than double that of men (19% versus

TABLE 5. Twenty-eight-day mortality rate among patients with NSTEMI-ACS and STE-ACS, stratified by gender

	Men, n (%)	Women, n (%)	Total, n (%)	p
NSTEMI-ACS group				
Short-term mortality (28 days)				
Deaths	812 (8.3)	433 (12.1)	1,245 (9.3)	< 0.001
Total	9,839	3,566	13,405	
STE-ACS group				
Short-term mortality (28 days)				
Deaths	2,387 (9.1)	1,564 (19.7)	3,951 (11.5)	< 0.001
Total	26,363	7,950	34,313	

TABLE 6. Predictors of in-hospital mortality, short-term mortality and long-term mortality among with NSTEMI-ACS based on logistic regression analysis

Variables	n-hospital mortality		Short-term mortality (28 days)	
	p	OR (95% CI)	p	OR (95% CI)
Female gender	0.543	1.05 (0.90-1.22)	0.827	1.02 (0.88-1.18)
Age	< 0.001	1.04 (1.04-1.05)	< 0.001	1.05 (1.04-1.05)
AHT	0.338	1.07 (0.94-1.22)	0.132	1.10 (0.97-1.25)
DM2	< 0.001	1.58 (1.39-1.81)	< 0.001	1.59 (1.40-1.80)
Tobacco use	< 0.001	0.67 (0.58-0.79)	< 0.001	0.66 (0.57-0.77)
Previous AMI	< 0.001	1.39 (1.22-1.60)	< 0.001	1.40 (1.22-1.59)
Beta-blockers	< 0.001	0.21 (0.18-0.26)	< 0.001	0.23 (0.19-0.27)
ACEI	< 0.001	0.40 (0.34-0.46)	< 0.001	0.42 (0.36-0.49)
Coronary angiography	0.003	0.71 (0.57-0.89)	0.045	0.81 (0.65-0.99)
Constant	< 0.001	0.01	< 0.001	0.01

ACEI: angiotensin-converting enzyme inhibitors; AHT: arterial hypertension; AMI: acute myocardial infarction; CI: confidence interval; DM2: type 2 diabetes mellitus; OR: odds ratio.

8.7%), a difference that was statistically significant. The 28-day mortality rate for the patients in the STE-ACS was slightly higher than that of the patients in the NSTEMI-ACS group. Among the patients who experienced an ST-elevation coronary event, the 29-day mortality rate 11.5%, and was more than 10 percentage points (double in relative terms) higher for women (19.7%) than for men (9.1%) ($p < 0.001$). Thus, while women had higher mortality rates than men in both groups, the observed differences between the genders were more marked among the patients in the STE-ACS group.

Factors predicting mortality among patients with ACS

We performed logistic regression analyses to identify the patient characteristics that could predict clinical outcomes. Various clinical variables were analysed to determine their effect on in-hospital mortality and short-term (28-day) mortality rates. Among the patients with NSTEMI-ACS, it was observed that female gender and hypertension did not influence mortality rates (table 6). The variables that were associated with a greater risk of in-hospital death were diabetes [odds ratio (OR) = 1.6], previous history of myocardial infarction (OR = 1.4), and older age (OR = 1.04). In terms of the other variables that were included in the model, the performance of a coronary angiography and treatment with ACEIs and/or beta-blockers were determined to be protective and to therefore reduce the risk of death. In the results, the “smoker’s paradox” that has been previously noted in other studies, can also be observed. With regard to 28-day mortality rates, neither female gender nor hypertension was found to independent predictors of mortality. However, the excess mortality that was

observed among the women in this study can be explained by other factors related to being female (table 6). Once again, diabetes (OR = 1.6), a previous history of myocardial infarction (OR = 1.4), and older age (OR = 1.04) were associated with higher short-term mortality rates. The utilisation of coronary angiography and administration of ACEIs and/or beta-blockers were found to be protective.

With regard to in-hospital mortality rates, among the patients in the STE-ACS group, delayed hospital admission the hospital after the onset of ACS symptoms, hypertension, and smoking status were not found to be associated with increased mortality rates on logistic regression analysis (table 7). In this group of patients, female gender was the factor that was found to most markedly increase the risk of death (OR = 1.6). Previous history of myocardial infarction (OR = 1.6), the reperfusion by angioplasty (OR = 1.5), diabetes (OR = 1.3), and older age (OR = 1.1) were also associated with increased in-hospital mortality rates. The administration of beta-blockers and/or ACEIs as well as the utilisation of coronary angiography and fibrinolysis were found to be protective and were associated with a decreased risk of death due to ACS during the hospitalisation period.

The factors that influenced the 28-day mortality rates of patients with STE-ACS were very similar to those that predicted in-hospital mortality. Hypertension, tobacco use, and a delay from the time of onset of ACS symptoms to hospital admission were not associated with 28-day mortality rates in this group. The variables that were found to increase the probability of death for a patient with ACS during the first month after the hospitalisation for STE-ACS were female gender (OR = 1.6), previous myocardial infarction (OR = 1.6), angioplasty (OR = 1.3), diabetes (OR = 1.3), and older age (OR = 1.1).

TABLE 7. Predictors of in-hospital mortality, short-term mortality and long-term mortality among with STE-ACS based on logistic regression analysis

Variables	In-hospital mortality		Short-term mortality (28 days)	
	p	OR (95% CI)	p	OR (95% CI)
Female gender	< 0.001	1.6 (1.4-1.9)	< 0.001	1.6 (1.4-1.9)
Age	< 0.001	1.1 (1-1.1)	< 0.001	1.1 (1-1.1)
AHT	0.5	1.1 (0.9-1.2)	0.8	1.0 (0.9-1.2)
DM2	< 0.001	1.3 (1.1-1.6)	< 0.001	1.3 (1.1-1.5)
Tobacco use	0.3	0.9 (0.8-1.1)	0.2	0.9 (0.7-1.1)
Previous AMI	< 0.001	1.6 (1.3-1.9)	< 0.001	1.6 (1.3-1.9)
Beta-blockers	< 0.001	0.3 (0.2-0.4)	< 0.001	0.3 (0.2-0.4)
ACEI	< 0.001	0.5 (0.4-0.6)	< 0.001	0.5 (0.4-0.6)
Coronary angiography	< 0.001	0.4 (0.3-0.7)	< 0.001	0.5 (0.4-0.7)
Admission delay	0.4	0.9 (0.8-1.1)	0.5	0.9 (0.8-1.1)
Fibrinolysis	< 0.001	0.8 (0.8-0.9)	< 0.001	0.7 (0.7-0.9)
Angioplasty	< 0.001	1.5 (1.2-2)	< 0.001	1.3 (1-1.7)
Constant	0	0	0	0

ACEI: angiotensin-converting enzyme inhibitors; AHT: arterial hypertension; AMI: acute myocardial infarction; CI: confidence interval; DM2: type 2 diabetes mellitus; OR: odds ratio.

DISCUSSION

In this study, we performed what is possibly the most extensive analysis that has been carried out regarding the influence of gender on the characteristics, evolution, management, and prognosis of patients with ACS in Spain. It includes information that was collected during a concrete period that began in 1994 and included patients that experienced ACS as late as 2002, when the PRIAMHO I⁸, DESCARTES and TRIANA 1 and 2 studies¹¹⁻¹³ were performed. It included 48,369 patients (13,405 with NSTEMI-ACS and 34,334 with STE-ACS), of which 24.3% were women (26.6% of the patients with NSTEMI-ACS and 23.2% of those with STE-ACS). Our analysis revealed that the women in this study had more unfavourable clinical characteristics and cardiovascular risk factors of than the men in this study had. In addition, we observed gender-related differences in the use of therapeutic and diagnostic resources in this population. Both of these factors may help explain the most significant finding of the research: the greater in-hospital and short-term mortality rates observed in women with NSTEMI-ACS as compared to men with NSTEMI-ACS. However, these same factors are cannot explain the excess mortality that was observed in women with STE-ACS with as compared to men with STE-ACS.

As was stated in the introduction, it is possible that ischaemic heart disease in women has unique characteristics that make it different from ischaemic heart disease in men, where these are not well known due largely to the insufficient inclusion of women in clinical trials and other studies⁶. The differences may

even include very basic clinical characteristics such as the clinical presentation of ACS. Ischaemic heart disease manifests itself as angina pectoris more frequently in women than in men, while men are more likely than women to present with AMI or sudden death. A similar proportion of women and men with ACS exhibit chest pain, but women report other cardiac symptoms more frequently than men do. Also of note, menopausal women are more likely to exhibit atypical symptoms than other patient groups. However, there are contradictory data for many aspects of the clinical presentation of ACS, such as the proportion of women that have classic presentations of ACS as well as the significance of an atypical angina in women. The cardiovascular history of ACS patients and their management also appear to differ by gender, as described below.

Differences in the clinical characteristics of men and women with ACS

This study shows that women with NSTEMI-ACS tend to be older than men with NSTEMI-ACS by an average of 6 years and also tend to have a much more unfavourable cardiovascular risk profile than the men in this group. Of note, women have a greater prevalence of arterial hypertension, dyslipidaemia, and diabetes, although their rate of tobacco use is lower than that of men. With regard to prior cardiovascular history, the proportion of women with a history of CVA or angina was similar to that of the men in the study, but the men had a greater atherosclerotic burden, as is shown by the greater frequency of prior myocardial infarction, coronary revascularisation

rates, and peripheral vascular disease that was observed among the males in this population. A prior history of heart failure was observed significantly less frequently among the women in this study, which is probably related to the older age of this group. In the STE-ACS group, gender-related differences were observed that were similar to those observed among patients with NSTEMI-ACS, although there were several differences noted. The mean age of the patients with ST elevation was greater than that of the NSTEMI-ACS group and women were 8.8 years older than the men in the STE-ACS group (as compared to 6 years older than the men in the NSTEMI-ACS group), but the prevalence of dyslipidaemia was similar between the two genders. These findings are similar to those of both international studies¹⁴⁻¹⁶ and studies that have been performed in Spain¹⁷⁻²¹. The RESCATE study¹⁸, which included 1,460 patients with myocardial infarction who were hospitalised in Catalonia between 1992 and 1994 and of whom 331 were women, found that the women in their study were significantly more likely to have had hypertension, diabetes, and previous episodes of angina than the men in the study, but were less likely to smoke. Marrugat et al¹⁷ observed the same findings in a large study (n = 22,836) that was comprised of patients various Spanish registries that contained information on patients with myocardial infarctions and unstable angina. It seems, therefore, that the differences observed between women and men in this study confirm the results of prior investigations. The older age of the women in these studies may at least partially explain the greater prevalence of comorbidities and the less favourable risk profile that they have at the time at which they suffer from ACS²². The lower prevalence of tobacco use that was observed among the women who suffered from ACS in this study could very likely be due to cultural factors, since in the general population fewer women than men, especially elderly women, smoke tobacco. Given that the women in this study were significantly older than the men, the differences in smoking rates that were found in this population are in line with the trends that are observed in the overall population.

Gender-related differences in the utilisation of diagnostic and therapeutic resources among patients with ACS

The rates of utilisation of antiplatelet and antithrombotic agents in the treatment of hospitalised patients with NSTEMI-ACS were high and were similar between men and women. The gender-related differences that were observed in treatments that were administered to the patients in this study (i.e., the lower utilisation of beta-blockers, statins, and percutaneous coronary interventions in women) cannot be clearly explained, since the baseline characteristics of the

patients indicated that the women in this study had a higher risk profile than the men in this study, and one would therefore expect them to receive more intensive treatments. A greater use of ACEI and diuretics was observed among the women in this study, which is probably related to the greater prevalence of arterial hypertension that was present as well as the higher incidence of cardiac failure that they experienced during their hospitalisation. In women with STE-ACS, as with those suffering from NSTEMI-ACS, differences were detected in the use of pharmacological interventions and of therapeutic resources. Considering the greater risk profile of the women in the study, this indicates a wider underutilisation of resources among women than men. The WISE¹⁵ and CRUSADE¹⁴ studies, which were performed in the United States, had findings that were somewhat similar to our findings in some respects, but not in others. In the American studies, women were less likely to receive the recommended pharmacological interventions (aspirin, heparin, glycoprotein IIb/IIIa inhibitors, ACE inhibitors, and statins) than men were and were also less likely to undergo diagnostic or therapeutic cardiac catheterisations. However, in our study, the use of antiplatelet agents, heparin, and ACE inhibitors was similar between genders or was greater in women. The gender-related differences that were observed in age at presentation of ACS could explain the differences in management and therapeutic interventions that were performed, since some of them are used with more caution in elderly patients²³. On the other hand, it is important to mention that more studies that specifically examine the benefit of different therapeutic treatments and strategies for women are needed, since it is clear that they are underrepresented in clinical studies^{5,6}.

The percentage of women with STE-ACS who underwent fibrinolysis for reperfusion was lower than that of men. This finding is common to all of the studies that have explored the differences in management between men in women, both in Spain and internationally^{14,15,17-19}. One of the studies, which was recently published and has already been mentioned, attributes the gender-related differences in the performance of fibrinolysis to the older age of the women in these studies, since there is a decrease in the probability of receiving early treatment that is associated with increasing age. In addition, the observed differences were unchanged when the results were adjusted for the presence of other comorbidities at the time of admission²⁰. Our findings of gender-related differences in the use of primary angioplasty between men and women are very debatable and should not be interpreted, since at the time the registries that were analysed were developed, the use of primary angioplasty had still not spread widely throughout Spain. Another notable observation was that there was a greater delay between the onset of

symptoms and hospital admission as well as between hospital admission and reperfusion for women than for men. The lag is produced by a greater delay both in admittance to the hospital (time from the onset of pain until admittance) and in the time between admittance and the beginning of reperfusion.

Gender-related differences in mortality rates among patients with ACS

Analysis of the patients with NSTEMI-ACS showed that the mortality rate and an incidence rate of adverse events (AMI, cardiac failure, and cardiogenic shock) during hospitalisation was 50% higher for women than for men with NSTEMI-ACS. The 28-day mortality rate was also high among patients with NSTEMI-ACS (9%), and was significantly greater among women than among men (12.1% vs. 8.3%, respectively). Among patients with NSTEMI-ACS, multivariate analysis showed that female gender was not independently associated with in-hospital or 28-day mortality. The excess of mortality that was observed among the women in this group can be explained by other factors that are frequently associated with female gender. Diabetes, previous myocardial infarction, and older age were all associated with an increased risk of death. The utilisation of coronary angiography, beta-blockers, and ACE inhibitors were found to be protective factors that were associated with a lower risk of mortality. There were differences observed between the patients with STEMI-ACS and NSTEMI-ACS. As with the patients with NSTEMI-ACS, female gender was an independent risk factor for in-hospital and 28-day mortality. The rate of death due to AMI was lower among women than among men in this study. However, it is notable that when one examines multiple hospital registries, the 28-day mortality rate is 20% higher among women than among men, even after adjusting for age, especially in countries that, like Spain, have a low incidence of ischaemic heart disease⁵. The analysis of the registries and the studies that analyse in-hospital mortality from myocardial infarction is complex because differences in study and registry designs make it difficult to perform comparative analyses. Marrugat et al⁵, in their review of the epidemiology of cardiovascular disease in women (which analysed the main existing studies on gender-related differences in CVD), found that women that are hospitalised for AMI are on average 10 years older, arrive at the hospital one hour later, have comorbidities, and have worse clinical courses than men who are hospitalised for AMI. However, after adjusting for the aforementioned risk factors, women still to have a higher 28-day mortality rate than men. The existing data from Spain confirms the results of our study. Two studies^{17,18} have shown that mortality is greater among women hospitalised for their first AMI,

even after adjusting for possible confounding variables, yet they have not demonstrated this finding for other presentations of ischaemic heart disease. The last of the studies that analyses gender-related differences in mortality rates among patients with AMIs that is referred to in one of the registries that was included in this study (PRIAMHO II)¹⁰ demonstrated that female gender is a negative prognostic factor with regard to 28-day mortality and a composite endpoint that included death, reinfarction, post-infarction angina, and CVA. Other national studies have demonstrated similar results^{24,25}.

Although female gender may independently influence patient prognosis, other factors exist that could partially explain the excess mortality that was observed among the women in this study. One possible explanation is the older age and higher rate of comorbidities that are associated with ischaemic heart disease that were present among the women in this study as well as the fact that women are more likely to have atypical presentations of CVD that tend to be less symptomatic than those of men²⁶. The atypical presentation may cause a delay in treatment as it may take the patient and her acquaintances longer to recognise the symptoms and their severity¹⁸. In addition, the atypical presentation can also delay the classification of women with ACS as patients in need of urgent and immediate care²³. Even after a woman has been diagnosed with ACS, the fact that women tend to be older, have more comorbidities, and worse coronary disease as well as the delay in diagnosis makes it less likely that she will be a candidate for certain treatments that have been demonstrated to improve the survival of patients with ACS^{22,23}. Interestingly, several socio-cultural factors related to gender have also been indicated as possible explanations for the delay in the transfer of the patient to a hospital centre, diagnosis, and treatment that women experience²⁵.

The finding that tobacco use is a protective factor with regard to short-term mortality (the “smoker’s paradox”) is one that has been previously observed. For many years, there was no satisfactory explanation for this finding. Several hypotheses had already been suggested, among them that there may have been differences in the baseline characteristics of the patients that were confounding the results. Previous studies have noted that smokers experience AMIs about a decade before non-smokers, which was thought to be of importance with regard to clinical outcomes. However, the risk was similar among smokers and non-smokers when the results were adjusted for patient age^{27,28}. The fact that smokers tend to have less severe ischaemic heart disease than non-smokers was also considered as a possible explanation²⁹ and was attributed to the fact that smokers with ACS were treated more aggressively than non-smokers at the time of admission.

Limitations

All studies have some limitations, but given the design of this and the methodology that was used in our analyses, it is especially relevant for the readers to take the limitations into account when interpreting the results. The main limitations of this study are:

– The data that are presented are from studies that were performed over a concrete time period (1994-2002); therefore, the clinical practices that were in place during the study period differ from current practices. Undoubtedly, treatment advances have been incorporated during that time that would have influenced the results had they been utilised during the study period, but more importantly, they have produced notable changes in patient management since 2002. The recommendations of international scientific societies regarding therapeutic strategies as well as pharmacological and mechanical interventions have changed since 2002 (the treatment guidelines of the main scientific societies have been updated twice since then). These changes, along with the expansion of the use of primary angioplasty and other types of interventional cardiology in the management of NSTEMI-ACS, as well as the increased efforts on the part of the scientific societies to achieve a better observance of the guidelines for the treatment of ACS, may have altered the gender-related differences that were observed in this study. Thus, the results of the MASCARA study will be key to understanding how the influence of gender has changed patient management in recent years.

– One of the most important limitations of this study is due to the methodology that was used to obtain the data. Because we had to construct a new database by fusing existing databases, only information that was available in all databases was able to be included in the final database, which led to the exclusion of a large quantity of clinical information.

– It is possible that bias was introduced when we divided the patients into two groups (NSTEMI-ACS and STEMI-ACS) due to the criteria that we used to allocate patients, which is described in the Methods section.

– In the case of NSTEMI-ACS, it is important to note that the majority of patients that were included came from myocardial infarction registries, and only that only small proportion of patients (from the DESCARTES study) had unstable angina. Since 2002, an infarction has been defined in patients with pain or troponin elevation.

Nevertheless, we believe that despite the aforementioned limitations, this study provides information of interest regarding the management of ACS in women during the study period.

CONCLUSIONS

This report identifies differences between men and women with ACS with regard to their clinical and demographic characteristics as well as their utilisation of therapeutic resources, which explains part of the excess mortality that was observed in women. Opportunities for improvement in the care of women with ischaemic heart disease exist, including the initiation of campaigns directed at women that seek to increase their awareness of ischaemic heart disease and inform them that it is a disease that affects women as importantly as do other diseases, such as breast cancer, which is already regarded as a major health issue among many women, do. These campaigns should also emphasize that ischaemic heart disease is preventable and has modifiable risk factors. Additionally, educational programs that change the attitude of both patients and healthcare providers appear to be necessary to improve early the identification of ACS in women and to optimise their treatment such that it is in accordance with the recommendations of the guidelines of the various scientific societies.

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Heart Failure in Women: Sex Differences in Spain

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Few studies have been carried out on the specific characteristics of heart failure in women. The proportion of women included in major clinical trials on heart failure is under 20%, while women account for almost half of all hospital admissions for heart failure. Consequently, increased understanding of the actual status of heart failure in women is needed. The aim of this study was to investigate possible sex differences in the prevalence, clinical characteristics, diagnostic assessment, treatment and short- and long-term prognosis of heart failure in Spain. We analyzed data from clinical and observational studies organized by the Section of Heart Failure, Heart Transplantation and Associated Therapies of the Spanish Society of Cardiology during the last 10 years in Spain (i.e., the PRICE, BADAPIC, RAIC and ATIICA studies). The prevalence of heart failure was similar in men and women (6.5% and 7%, respectively). Among patients admitted with acute heart failure (RAIC study), women were older than men, were more likely to have a history of hypertension or diabetes mellitus, were less likely to have a history of coronary heart disease, and were more likely to have heart failure with preserved systolic function. Cardiac catheterization was performed in a smaller proportion of women and they received beta-blockers less frequently. In-hospital mortality and mortality 3 months after discharge were similar in men and women. The demographic, pathophysiological and clinical characteristics found in outpatients with chronic heart failure (BADAPIC study) were similar to those observed in the RAIC study: a smaller proportion of women than men received beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists, and lower doses were given. Long-term survival was similar in men and women, though women were more frequently admitted for decompensated heart failure. In the ATIICA study, female sex was found to be an independent predictor of low ACE-inhibitor, but not beta-blocker, use.

Key words: *Heart failure. Sex differences. Prevalence. Prognosis.*

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Insuficiencia cardíaca en la mujer. Diferencias de sexo en España

Las características específicas de la insuficiencia cardíaca en la mujer han sido poco estudiadas. La proporción de mujeres incluidas en los grandes ensayos clínicos sobre insuficiencia cardíaca es inferior al 20%, mientras que casi la mitad de los ingresos hospitalarios por este problema son de mujeres. Por ello, es importante conocer cuál es la realidad de la insuficiencia cardíaca en mujeres en nuestro entorno. El objetivo de este trabajo es evaluar las posibles diferencias por sexo en la prevalencia, las características clínicas, las medidas diagnósticas, el tratamiento y el pronóstico a corto y largo plazo de la insuficiencia cardíaca en España. Para ello, hemos analizado los estudios y registros de la Sección de Insuficiencia Cardíaca, Trasplante Cardíaco y otras alternativas terapéuticas de la Sociedad Española de Cardiología realizados en los últimos 10 años en nuestro país (estudios PRICE, BADAPIC, RAIC y ATIICA). Las prevalencias de insuficiencia cardíaca en mujeres y varones fueron similares (el 7 y el 6,5%, respectivamente). Entre los pacientes ingresados por insuficiencia cardíaca (estudio RAIC), las mujeres tienen mayor edad, más antecedentes de hipertensión arterial y diabetes y menos de cardiopatía isquémica, y mayor proporción de casos con función sistólica conservada. Se realizan en ellas menos cateterismos cardíacos que en los varones y se utilizan con menor frecuencia fármacos como los bloqueadores beta. La mortalidad durante el ingreso y a los 3 meses del alta fue similar en mujeres y varones. En pacientes seguidos ambulatoriamente (estudio BADAPIC), las características demográficas, clínicas y fisiopatológicas son similares a las encontradas en el estudio RAIC; las mujeres con insuficiencia cardíaca recibieron bloqueadores beta, inhibidores de la enzima de conversión de angiotensina y antagonistas del receptor de la angiotensina II en menor proporción que los varones y a dosis más bajas. La supervivencia a largo plazo fue similar en mujeres y varones, aunque las mujeres tuvieron una mayor incidencia de ingresos por descompensación de la insuficiencia cardíaca. En el estudio ATIICA, el sexo femenino fue predictor independiente de un menor uso de inhibidores de la enzima de conversión de angiotensina, pero no de bloqueadores beta.

Palabras clave: *Insuficiencia cardíaca. Diferencias de sexo. Prevalencia. Pronóstico.*

INTRODUCTION

Cardiovascular disease is the leading cause of death in developed countries and consists primarily of ischaemic heart disease and cerebrovascular disease. Congestive heart failure (CHF) is the third leading cause of death from cardiovascular disease in Spain in addition to being a major cause of morbidity and hospitalisation¹⁻³. The number of women who die from cardiovascular disease is almost twice that of men. The mortality rates for heart failure increase with age in both genders, with very low CHF-associated mortality rates observed before the age of 60. However, the absolute number of CHF-related deaths is two-fold higher in women than in men because of the different age distribution of the genders (i.e., the female population is older than the male population). CHF is responsible for 4-8% of deaths from all causes and 12-20% of deaths from cardiovascular disease in both males and females.

With the increase of life expectancy that has occurred in our population in recent years and the improved treatment options available for ischaemic heart disease and arterial hypertension, CHF is of particular relevance given its increasing prevalence. Despite the advances that have been made in the treatment of CHF and the improvements that have been made in our understanding of its pathophysiology, the reduction in the CHF-related mortality rate has been only modest. Certain health problems appear to be unique to women, and others occur more frequently and even disproportionately in women, such as breast cancer, rheumatoid arthritis, and osteoporosis. Nevertheless, it is important to remember that cardiovascular disease remains the leading cause of death in women. However, the characteristics of this disease in women have been less well studied than they have been in men. For instance, in large clinical trials of CHF, only about 20% of the subjects were women. However, 50% of hospitalisations for CHF in the overall population are of women, indicating that women were markedly underrepresented in those clinical trials.

Conflicting data have been reported in the past several decades regarding the evolution of the incidence of CHF in our environment has been reported in the last few decades. Many of the studies that have presented this data were epidemiological studies that were performed in the United States. In the Framingham study⁴, the incidence of heart failure in women was found to have declined by nearly a third between 1950 and 1990 but had remained the same among males during the same period. This is attributed to improvements that have been made in the diagnosis and treatment of arterial hypertension, which is the main cause of CHF in women, as well as the decrease of the incidence of rheumatic heart disease in the past several decades. In

the Framingham cohort, mortality from CHF has dropped in both women and men, although the 5-year survival rate is still only 50% for these patients, despite the major advances that have been made in the treatment of CHF. However, the data from the Rochester study⁵ do not show a decrease in the incidence of CHF in women. The results of this study show that there has been a modest improvement in survival, which was less marked in women than in men. In a closed environment in the 1990s, the mortality rate after hospitalisation for CHF in Scotland appeared to decrease in both men and women⁶. However, hospitalisation rates for CHF in the United States continue to increase, especially among women and the elderly⁷.

OBJECTIVES

In this report, we attempted to review the available evidence regarding gender differences in the diagnosis and treatment of CHF in our country. Our main objectives were to:

- Study the prevalence of heart failure in men and women in Spain.
- Determine the clinical, aetiological, and prognostic characteristics of heart failure in each gender in Spain and in distinct populations (e.g., outpatients and patients admitted for decompensated CHF).
- Evaluate whether the quality of care for patients with heart failure (as assessed by the conduction appropriate diagnostic tests, pharmacological, and non-pharmacological treatments, and so on) in Spain differs with respect to gender.

In order to achieve these objectives, we analysed a prevalence study (PRICE), a hospital record database (RAIC), an ambulatory record (BADAPIC), and the ATIICA study.

THE PREVALENCE OF HEART FAILURE IN SPAIN (THE PRICE STUDY)

In Spain, the only available study examining the prevalence of CHF was performed in the Asturias⁸ population and did not evaluate gender differences. Recently, there was a prevalence study conducted in different health centres and hospitals around Spain that included all individuals over 45 years of age in the entire national territory. However, the results of this study have not yet been published (M. Anguita, personal communication). The study used a stratified random selection by age and gender from the population assigned to each health centre. The primary care physician at the health centre used the Framingham⁹ criteria to diagnose CHF, which requires in the presence of two of a number of major criteria

TABLE 1. Prevalence Data of the PRICE study

	%	95% CI
Men	6.5	4.7-8.4
Women	7.0	4.4-9.6
Age (years)		
45-54	1.3	0.1-3.3
55-64	5.5	2.4-8.5
65-74	8.0	4.2-11.8
> 74	16.1	11-21.1
Total	6.8	4.9-8.7

(nocturnal paroxysmal dyspnoea, orthopnoea, jugular venous distension, rales, third heart sound on cardiac auscultation, cardiomegaly on chest radiograph, radiographic pulmonary oedema) or one major and two minor criteria (leg oedema, nocturnal cough, dyspnoea on exertion, hepatomegaly, pleural effusion, heart rate > 120 beats/min, loss of > 4.5 kg after 5 days of diuretic therapy) for the diagnosis of heart failure to be made. A patient was referred to a cardiologist for further evaluation if criteria for CHF (for complete review and confirmation/exclusion of the diagnosis) were present. An echocardiogram was performed if diagnostic doubts existed. The study also included a subset of patients who did not meet the criteria for a diagnosis of CHF, where this subset of patients served as a control group. This study included 1,776 people in 15 hospitals (990 women, 55.9%). A total of 242 people were sent for further evaluation by a cardiologist.

The prevalence of CHF was found to increase with age (table 1) and there were no statistically significant differences between men and women in any age group with regard to CHF prevalence. The diagnostic agreement between the primary care physicians and the cardiologists in the subsample that was seen by both types of physician was high (86%, 89.7% for exclusion of the diagnosis of CHF, and 72% for CHF diagnosis). The kappa coefficients were somewhat smaller, since the kappa index depends largely on disease prevalence, which was low in this population.

CHF MANAGEMENT IN SPAIN BASED ON THE ANDALUSIAN HEART FAILURE REGISTRY (RAIC REGISTRY)

Gender differences in the diagnostic and therapeutic management of CHF in Spain can be studied from the perspective of a hospital registry of patients who were admitted with a primary diagnosis of heart failure. We examined the results of a study on this topic that was recently published using data from the Andalusian Heart Failure Registry (RAIC)¹⁰. This included a total of 795 patients who were prospectively enrolled in the study. At each of the 16 participating hospitals, 50 consecutive

TABLE 2. Demographic characteristics of the RAIC registry patients, stratified by gender

	Men (n = 430)	Women (n = 365)	p
Age, years-	69.4 ± 11	73.4 ± 10	< 0.001
Age > 75 years, %	35	50.4	< 0.001
Cardiology/internal medicine, %	64/34	54/42	< 0.02
Hypertension, %	63	74	< 0.004
Hyperlipidaemia, %	33	32	NS
Diabetes, %	41.2	50.7	< 0.007
MI, %	29	16	< 0.001
Renal failure, %	21	16	0.07

MI: acute myocardial infarction; NS: not significant. Data are expressed as a total percentage of each group or as a mean ± standard deviation.

TABLE 3. The left ventricular function, prevalence of atrial fibrillation, and aetiology of heart failure of the RAIC registry patients, stratified by gender

	Men (n = 430)	Women (n = 365)	p
EF < 45%	57	36	< 0.001
Atrial Fibrillation	42	49	< 0.01
Ischemic Aetiology	46	26	< 0.001
Hypertensive Aetiology	32	47	< 0.001

EF: ejection fraction. Data are expressed as a total percentage of each group.

registry participants who were admitted to any department or unit in the hospital between May and July 2004 (all levels of care, integrated in the Andalucía public health network) with a primary diagnosis of CHF as defined by the criteria of the European Society of Cardiology. These criteria require the presence of two of the following criteria (and a third used in equivocal cases): symptoms and signs of heart failure at rest or during exercise; evidence of left ventricular dysfunction at rest; and response to heart failure treatment to make a diagnosis of CHF. This study presented the demographic characteristics (age, gender, and cardiovascular risk factors), clinical features [CHF aetiology, previous drug regimens, prior heart failure episodes, chronic renal failure (defined as creatinine > 2 mg/dl), and other comorbidities], results of complementary tests that had been performed (EKG, laboratory studies, radiological studies, echocardiography, cardiac catheterisation, and ischaemia induction tests), pharmacological treatments received prior to discharge, and in-hospital complications of the included patients over the in three-month study period.

The main patient characteristics that were examined in the study are described in tables 2-6. The presentation of CHF did not differ between men and women in this registry and were similar to different

TABLE 4. Additional investigations performed during hospitalisation or preceding six months among the RAIC registry patients

	Men (n = 430)	Women (n = 365)	p
Electrocardiogram	100	100	NS
Analytical	100	100	NS
Chest Radiology	100	100	NS
Ergometry	16.3	10.7	< 0.01
Catheterisation	22	18	< 0.01
Echocardiogram	99	99	NS

NS: not significant.
Data are expressed as a total percentage of each group.

TABLE 5. Analysis of the differences in the pharmacological treatment of the RAIC registry patients by gender

	Men (n = 430)	Women (n = 365)	p
Diuretics	93	95	NS
Digoxin	54	46	NS
ACE/ARB prior	57	59.2	< 0.01
ACE/ARB high	85.3	78.4	< 0.01
Beta Blockers	53	38	< 0.001
Anticoagulants	42	3.6	NS

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; NS: not significant.

TABLE 6. Factors predicting the use of beta blockers among the RAIC registry patients

	RP	95% CI	p
Hypertension	1.47	1.04-2.07	0.02
Previous myocardial infarction	1.79	1.13-2.83	0.01
EF < 40%	1.58	1.15-2.18	0.004
Age > 75 years	0.51	0.37-0.70	0.001
Female gender	0.68	0.49-0.94	0.02
COPD	0.51	0.35-0.74	0.001

CI: confidence interval; COPD: chronic obstructive pulmonary disease; RP: risk probability.

those described in previous publications in that were performed other settings and examined the diagnosis and therapeutic management of CHF¹¹⁻¹⁴. The women who are admitted to a hospital for heart failure are usually older than the men. The percentage of female patients over 75 years of age that were included in the study was particularly striking: they are underserved by the cardiology service, more likely to be diabetic and/or hypertensive, and less likely to have an ischaemic aetiology their CHF than men. In addition, the left ventricular ejection fraction was preserved in a greater percentage of women than men. The small gender-related differences that were observed in the additional tests that were performed (namely cardiac

catheterisation and exercise testing) may be related to differences in the main aetiology of the CHF. There were no gender-related differences with regard to hospital mortality (5.2%) or short-term morbidity (19.2%) in this study. The pharmacological treatments received by patients in this registry are especially interesting, especially taking into account the extensive scientific evidence that the use of vasodilators and beta-blockers is beneficial in patients with left ventricular dysfunction and the fact that there is much less evidence of benefit if patients' left ventricular function is preserved. The rate of use of vasodilators was 82% and 46% of patients were taking beta-blockers. The gender differences may be explained by differences in aetiology of CHF that exist between men and women. However, in a multivariate analysis examining predictors of the use of beta-blockers, it appears that female gender was associated with a decreased utilisation of beta-blockers. In a similar analysis examining predictors of the utilisation of vasodilators, this was not the case, which is interesting, as some have studies shown that vasodilators have a smaller beneficial effect in women¹⁵. This finding has also been described for digoxin. The percentage of patients taking oral anticoagulants was very similar to the percentage of patients with atrial fibrillation in this registry.

EVALUATION OF THE AMBULATORY CARE OF CHF PATIENTS BASED ON A SPANISH REGISTRY OF AMBULATORY PATIENTS THAT WERE EVALUATED BY SPECIALISTS FOR THEIR CHF (BADAPIC REGISTRY)

Another area in which gender differences among CHF patients should be assessed is the ambulatory setting. To do so, we analysed data from the BADAPIC registry¹⁶. This is a voluntary official registry created by the Section of Heart Failure, Cardiac Transplant, and other therapeutic alternatives of the Spanish Cardiology Society that was launched in 2000 by the Working Group on Heart Failure. In order to participate in the registry, patients had to be seen in a separate consultation for their CHF. All patients were included in a common database with the agreement of all participating centres. Data collection has been performed annually at the end of each year since the registry was created in 2000. The data presented in this study pertains to the data that was reported between 2000 and 2003. During this time period, 4,720 patients were seen for CHF consultation in 62 specialty centres throughout Spain and had an average follow-up of 40 ± 12 months. Because this patient population was followed in specialised units that mostly comprised cardiologists who specialised in CHF, there was an obvious selection bias in this study. However, the outcomes of these patients are quite

TABLE 7. Demographic characteristics of the BADAPIC registry patients, stratified by gender

	Men (n = 3,351)	Women (n = 1,369)	p
Age (years)	64 ± 12	70 ± 12	< 0.001
Arterial Hypertension	35	50	< 0.001
Hyperlipidaemia	42	34	NS
Diabetes	29	39	< 0.001
Ischaemic heart disease	50	30	< 0.001
Previous myocardial infarction	41	19	< 0.001
Coronary revascularisation	20	9	< 0.01

Data are expressed as a total percentage of each group or as a mean ± standard deviation.

TABLE 8. Characteristics of the BAPAPIC registry patients

	Men (n = 3,351)	Women (n = 1,369)	p
Class III-IV HF	53	35	0.0002
LVEF	38 ± 17	47 ± 24	< 0.001
EF < 45%	73	40	< 0.001
Sinus rhythm	68	62	< 0.05
Aetiology IHD	48	26	< 0.001
Aetiology HTN	12	29	< 0.001
Aetiology DCM	18	6	< 0.05

DCM: dilated cardiomyopathy; HF: heart failure; HTN: arterial hypertension; IHD: ischaemic heart disease; LVEF: left ventricular ejection fraction. Data are expressed as a total percentage of each group or as a mean ± standard deviation.

TABLE 9. Additional investigations conducted among patients in the BADAPIC registry

	Men (n = 3,351)	Women (n = 1,369)	p
Ergometry	22	9	< 0.05
Isotopes	21	13	< 0.05
Holter monitor	25	20	NS
Catheterisation	49	30	< 0.01
Echocardiogram	90	88	NS
Known EF	97	93	NS

EF: ejection fraction. Data are expressed as a total percentage of each group.

TABLE 10. Analysis of differences in the pharmacological treatment of BADAPIC registry patients by gender

	Men (n = 3,351)	Women (n = 1,369)	p
Diuretics	85	90	NS
Digoxin	48	49	NS
ACE	82	70	< 0.001
ARB	27	18	< 0.01
Spirolactone	43	43	NS
Beta Blockers	75	62	< 0.001
Anticoagulants	44	44	NS
Antiplatelet agents	47	41	< 0.02

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

generalisable to the overall CHF population in this region of Spain. Gender differences in the baseline characteristics, complementary tests that were performed, and the pharmacological treatments that were received by the patients in this analysis are described in tables 7-10. Men were younger than women (64 ± 12 vs. 70 ± 12 years), were less likely to have a history of arterial hypertension, diabetes, or hyperlipidaemia, and were more likely to have a history of ischaemic heart disease and to have undergone coronary revascularisation. The mean left ventricle ejection fraction (LVEF) of the men in the study was significantly lower than that of the women (38% ± 1% vs. 47% ± 24%; p < 0.001). A total of 73% of males had evidence of ventricular systolic dysfunction (defined as LVEF < 45%) as compared to 40% of the women, where this difference was statistically significant. Most patients (65%) were found to be sinus rhythm when electrocardiograms were performed. The distribution of CHF aetiology shows that ischaemic heart disease was the predominant cause of CHF in this patient population (39%), followed by hypertension (18%), idiopathic or enol (17%), and valvular (11%). The remaining 15% of patients had CHF induced by other causes, including acute myocarditis, arrhythmias, congenital heart disease, restrictive or hypertrophic cardiomyopathy, or other specific aetiologies. The ischaemic and idiopathic-enol aetiologies were significantly more common in males, whereas in females, hypertension was more common. No significant gender differences were observed for the other causes of CHF that were examined in this study (table 8). There were no differences regarding the rate of utilisation of Doppler echocardiogram or ambulatory Holter electrocardiogram monitoring. Males were significantly more likely to have received the tests that were included in this study: stress testing by ergometry (22 vs. 9%), isotopic studies (21 vs. 13%) and cardiac catheterisation (49 vs. 30%). These differences may be justified by the different aetiologies of CHF that were observed between the men and women in this study.

The pharmacological treatments that patients received after their initial CHF consultation are shown in table 10 (stratified by gender). There were no significant gender differences seen in prescription of diuretics, digitalis, spironolactone, or anticoagulants. In contrast, we found that men were significantly more likely to have been prescribed beta-blockers (75 vs. 62% in women; p < 0.001), angiotensin converting enzyme (ACE) inhibitors (82 vs. 70% in women; p < 0.001), angiotensin receptor blockers (ARBs) (27 vs. 18% in women; p < 0.01), and anti-platelet agents (47 vs. 41% in women; p = 0.011). Males were also found to be taking a significantly higher average dosage of enalapril and carvedilol (16 ± 11 mg/day of enalapril

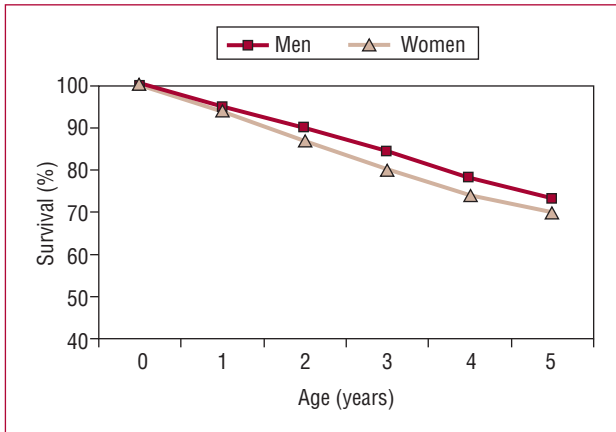


Fig. 1. Probability of overall survival during the follow-up period in the BADAPIC study, stratified by gender.

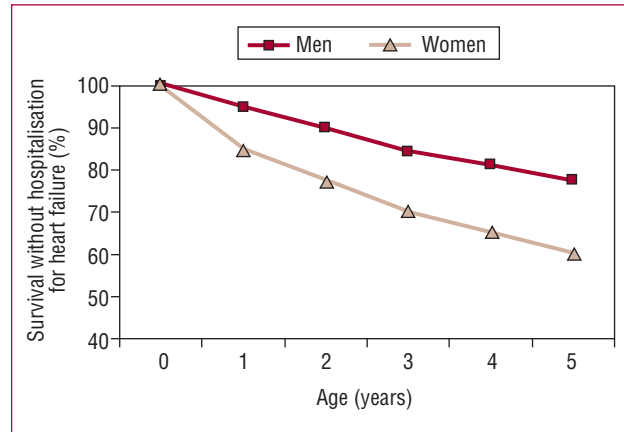


Fig. 2. Probability of survival without hospitalisation for heart failure during the follow-up period for patients in the BADAPIC study, stratified by gender.

TABLE 11. Differences between men and women in the ATIICA study regarding the objectives of general measures and diagnostic tests

	Men (n = 3,351)	Women (n = 1,369)	p
Low Sodium Diet	83.3	84.0	NS
Exercise	58.7	59.0	NS
Ideal Weight	35.1	34.6	< 0.001
EF Evaluation	88.0	86.0	NS
Coronary Angiography	83.0	83.0	NS

EF: ejection fraction; NS: not significant. Data are expressed as a total percentage of each group.

in men vs. 14 ± 12 mg/day in women and 22 ± 16 mg/day of carvedilol in men vs. 19 ± 16 mg/day in women). No significant gender differences were observed in the dosage of other medications.

The overall survival rates in relation to gender, after a mean follow up period of 40 ± 12 months, are shown in figure 1, and were similar in both men and women (73 and 70%, respectively; $p = NS$). There were significant differences in the overall survival rates without readmission for CHF during the follow up period (fig. 2). A total of 23% of men were readmitted in the hospital for CHF during the follow-up period, whereas 40% of the women in the study were readmitted during the follow-up period ($p < 0.001$).

EVALUATION OF THE QUALITY OF CHF CARE IN SPAIN (ATIICA STUDY)

New approaches to the diagnosis and treatment of patients with CHF lead to the implementation of interventional studies. The results of the ATIICA study that was performed in Spain were recently reported. This study was conducted by a cardiology service and analysed 1,000 patients with CHF who were discharged from 24 hospitals nationwide during the

TABLE 12. Analysis of differences in the pharmacological treatment of patients in the ATIICA study by gender

	Men (n = 3,351)	Women (n = 1,369)	p
Diuretics	98	98	NS
Beta Blockers	83.7	74.5	< 0.01
Maximum dosage of beta blockers	29	23	NS
ACE	91.4	83.5	< 0.01
Maximum dosage of ACE	33.4	31.6	NS
Spironolactone	83	81	NS

ACE: angiotensin-converting enzyme inhibitor; NS: not significant. The dosages are expressed in mg/day. The maximum dosage of beta-blockers is considered to be 10 mg/day of bisoprolol or nebivolol or 25 mg/day of carvedilol. The maximum dosage of ACE inhibitors is considered to be 20 mg/day of enalapril or ramipril and 75 mg/day of captopril or any other equivalent agent.

third quarter of 2004. A total of 16 quality indicators [percentage of patients who had their ejection fractions (EF) evaluated during the admission, the medications prescribed at discharge (ACE inhibitors and beta blockers, specifically), hygiene recommendations, and diet recommendations, referred to “ideal” patients] were examined in this population. A total of 38.7% of the patients in this study were female and on average, they were older than the included males, making this patient population similar to those included in previous studies. There were no gender differences regarding the utilisation of non-pharmacological measures, the rates of conduction of coronary angiography, or the evaluation of patients’ EF (table 11). Regarding the pharmacological treatments that patients received at the time of discharge, women received beta-blockers and ACE inhibitors less often than men (table 12). On multivariate analysis, the independent predictors for ACE inhibitor utilisation were female gender (odds

ratio [OR] = 0.59; 95% confidence interval [CI], 0.36-0.95; $p < 0.05$) and depressed EF (OR = 1.94; 95% CI = 1.1-3.1; $p < 0.01$). Regarding beta-blocker utilisation, the independent predictors identified on multivariate analysis were younger age (OR = 0.95; 95% CI = 0.94-0.97; $p < 0.01$) the presence of ischaemic heart disease (OR = 1.84; 95%CI = 1.26-2.78; $p < 0.05$). There were no gender differences identified with respect to the prescription of beta-blockers at the time of hospital discharge.

CONCLUSIONS

There are gender-related differences in the management of patients with CHF in Spain. These differences are largely due to epidemiological factors: women have a longer life expectancy than men, so the overall prevalence and number of CHF-related deaths are both higher in women than in men. The most common cause of CHF in men remains ischaemic heart disease, which likely justifies the higher number of diagnostic tests that tend to be conducted on men (especially tests to detect myocardial ischaemia and coronary angiography).

Arterial hypertension is presently the most prevalent risk factor in patients with heart failure and hypertension contributes to a large number of cases of CHF, especially in women. Given the gender-related differences in the clinical presentation, disease burden, aetiology, and hospitalisation rates of patients with CHF, the benefits and impact on disease progression, morbidity, and mortality of available heart failure treatments among different patient groups with different disease characteristics. In addition, with new methodological tools, it has become easier to better understand the differences in the management and treatment of patients with CHF.

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Hypertension in Spanish Women: Analysis of Data Collected by the Spanish Society of Cardiology Section of Arterial Hypertension

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This article reports the results of an analysis of the sex differences found in data from clinical and observational studies organized by the Section of Arterial Hypertension of the Spanish Society of Cardiology during the last 10 years in Spain (i.e., the VIIDA, VALYCOR, VALOR, KORAL-CARDIO, CAROL, REFRACVAS, CLYDIA and PAMISCA studies). The data collected covered around 50,000 hypertensive patients, of whom some 45% were female, and included almost all the different forms of hypertension encountered in patients with a wide range of cardiovascular disease. Although the studies analyzed had different objectives and, therefore, different designs, taken together they were very similar, and their results are therefore clinically comparable. Overall analysis indicated that the hypertensive women included in the different studies had a more unfavorable cardiovascular risk profile than men. However, there were a number of sex differences in diagnosis and therapy that could explain, at least in part, why cardiovascular disease has a poorer prognosis in women. Blood pressure control is poor in Spain, in both men and women. As a whole, these findings can provide the basis for devising specific programs or actions aimed at correcting this situation.

Hipertensión arterial en la mujer en España: análisis de los registros de la Sección de Hipertensión Arterial de la Sociedad Española de Cardiología

Se presentan los resultados del análisis por sexos de los registros y estudios de la Sección de Hipertensión Arterial de la Sociedad Española de Cardiología realizados en los últimos 10 años en España (VIIDA, VALYCOR, VALOR, KORAL-CARDIO, CAROL, REFRACVAS, CLYDIA y PAMISCA). Estos registros incluyen aproximadamente a 50.000 pacientes, de los que el 45% son mujeres, y abarcan casi todo el espectro de la hipertensión arterial en los diferentes escenarios de la enfermedad cardiovascular. Aunque los estudios analizados tienen diferentes objetivos y, por lo tanto, distintos diseños, en conjunto presentan una gran similitud, por lo que sus resultados son comparables desde el punto de vista clínico. Del análisis general se puede concluir que las mujeres hipertensas incluidas en los diferentes estudios tienen un perfil de riesgo cardiovascular más desfavorable que el de los varones. Además, hay diferencias en el enfoque diagnóstico y terapéutico que podrían justificar, al menos en parte, el peor pronóstico de la enfermedad cardiovascular en las mujeres. El grado de control de las cifras de presión arterial es pobre en nuestro país, tanto en varones como en mujeres. Todos estos datos pueden servir de base para desarrollar programas o acciones específicas para tratar de corregir esta situación.

Key words: Arterial hypertension. Sex differences. Prognosis.

Palabras clave: Hipertensión arterial. Diferencias de sexo. Pronóstico..

INTRODUCTION

Over the last few years, the Arterial Hypertension Chapter of the Spanish Cardiology Society has conducted various censuses of hypertensive patients with different comorbidities in order to fundamentally

understand the prevalence, clinical characteristics, and degree of hypertension control, all for including patients seen in routine practice. Even though there are differences in timing, scope, and the different evaluated factors, the obtained results, specific for each gender, are superimposable for the majority of parameters and allow for a joint analysis. However, the interest of this Chapter is not exclusively focused on arterial hypertension (AHT) because the total risk of vascular disease must be considered. From this perspective, the

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TABLE 1. Records of the Arterial Hypertension Chapter in this article

Study	Topic	n	Women, n (%)
VIIDA	AHT + LVH	16,123	7,795 (48)
VALOR	AHT + HR	9,533	4,623 (48.5)
VALYGOR	AHT + DYSF	4,000	2,080 (52)
KORAL-CARDIO	AHT + ALB	2,711	1,220 (45)
CAROL	AHT + HR + C	657	278 (42)
REFRECVAS	AHT resistant	15,217	6,086 (40)
Total AHT	—	48,239	22,082 (45.7)
CLYDIA	MS	1,313	400 (31)
PAMISCA	PAD/ACS	1,424	403 (35)

ALB: albuminuria; C: control; DYSF: cardiac dysfunction; HR: high risk; LVH: left ventricular hypertrophy; MS: metabolic syndrome; PAD/ACS: peripheral artery disease/acute coronary syndrome.

chapter also considers other studies to better understand the vascular risk and damage to our patients, for which the results of the CLYDIA (metabolic syndrome) and PAMISCA (peripheral arterial disease) studies are independently presented in detail.

ANALYSED REGISTRIES

The following is a brief description of each of the arterial hypertension studies. Their results are jointly analysed with respect to gender differences, given that the obtained data are superimposable for the majority of the evaluated factors (table 1).

VIIDA Study. Study of the prevalence and characteristics of patients with hypertension and left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a marker of cardiac damage in patients with hypertension and is also

a risk factor for cardiovascular and cerebrovascular disease. Because these conditions lower arterial pressure, all antihypertensive medications have the ability to reduce LVH, although not in the same magnitude even with equivalent changes in blood pressure¹. The clinical trial LIFE², published in 2002, showed that the greatest benefit was achieved in these patients with a therapeutic regimen based on an angiotensin II receptor blocker (ARB-II), specifically losartan, compared with a beta blocker, atenolol.

The VIIDA study is an observational epidemiological study combined with an educational program conducted in three sections at different times with the objectives a) to assess the prevalence of LVH in hypertensive patients seen in a cardiology consult and b) to describe the clinical management and degree of AHT control. The three sections were conducted during different periods of the years 2003 and 2004, when new clinical practice guidelines for the treatment of AHT had already been published and promoted. Two hundred physicians participated, who were asked to include 10 consecutive hypertensive patients in each section that showed LVH on their EKG in accordance with the Sokolow-Lyon criteria (sum of R wave in V5-6 plus S wave in V1 > 35 mm) or the Cornell voltage criteria (sum of R wave in aVL plus S wave in V3 > 20 mm in women or >28 mm in males) or both, estimating that each physician would study approximately 50 hypertensive patients. Between April 2003 and November 2004, 19,532 patients were assessed in three separate sections, of which 3,409 were excluded; 4,037 presented with LVH, which signifies a prevalence of 25%. Of the studied patients, 48.35% were women, and differences were seen in the presence of LVH according to the criteria used, gender, and the presence of diabetes mellitus (fig. 1).

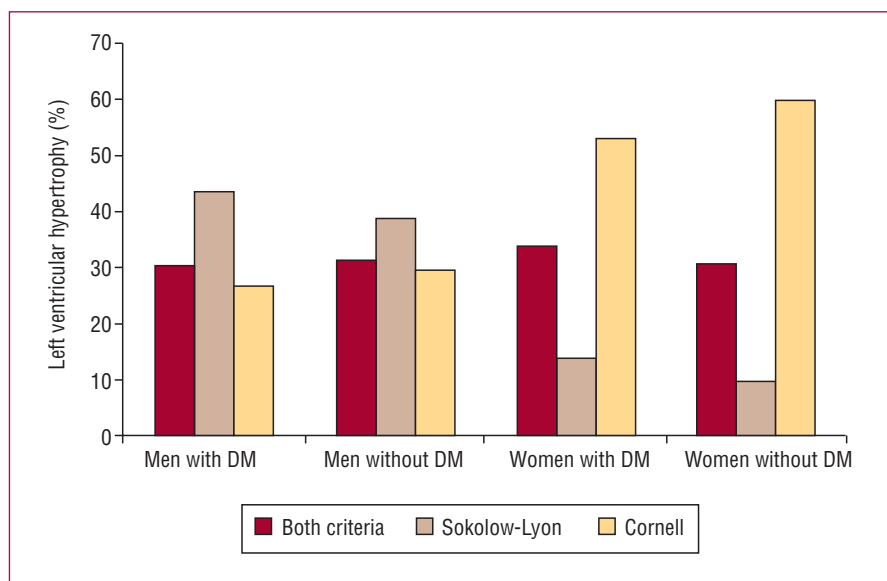


Fig. 1. Prevalence of left ventricular hypertrophy in VIIDA study patients; differences according to criteria (Sokolow-Lyon or Cornell), gender, and presence of diabetes mellitus (DM).

TABLE 2. Algorithm for the stratification of risk for the VALUE study

Age (years)	Men	Women
50-59	At least three risk factors or one disease	At least three risk factors and one disease or at least two diseases
60-69	At least two risk factors or one disease	At least two risk factors or one disease
> 70	At least one risk factor or one disease	At least one risk factor or one disease

VALYCOR Study. Arterial hypertension and cardiac dysfunction

AHT is the main determinant of cardiovascular diseases in Spain, among which cardiac insufficiency stands out. The prevalence and incidence of cardiac insufficiency is on the rise, which relates to the progressive aging of the population and also with the course of other cardiovascular diseases, such as ischemic cardiomyopathy, atrial fibrillation, and LVH, all of which are directly related to AHT. The VALYCOR³ study aimed to characterise a large group of hypertensive patients with cardiac dysfunction who presented with electrocardiographic criteria of LVH and clinical or radiological evidence of cardiac insufficiency and/or atrial fibrillation in addition to their AHT. In addition to knowing their clinical profile, clinical management, degree of control of blood pressure and associated risk factors, and utilised therapeutic strategies were evaluated. The usefulness of a questionnaire was assessed in patients with cardiac insufficiency and an EKG study that permitted the finding of clinical differences in association with the presence or absence of left ventricular systolic dysfunction. Because the study was conducted in the majority of autonomous Spanish communities and both in primary care and specialised consultations, the regional differences and of areas of assistance were explored. Between October 2003 and February 2004, 4,038 patients were recruited, of which 4,000 were analysed (23.2% in primary care and 76.8% in specialised care). Women made up 51.8% of the studied population.

VALOR Census. Study of prevalence and clinical characteristics of high-risk hypertensive patients

The clinical relevance of AHT does not reside in its characteristics as a disease but in the increase in vascular disease risk. The prevalence of AHT in our country is estimated to be approximately 25% of individuals 18 years of age and older, but it increases in relation to age and is higher than 50% in individuals older than 65. There is no knowledge of the prevalence of AHT and its treatment in high-risk patients (i.e., those that, in addition to AHT, also have diabetes

mellitus, hypercholesterolemia, LVH, proteinuria, or serum creatinine of 150 to 256 $\mu\text{mol/L}$, or are active smokers). In this group of patients, the VALUE⁴ study, published in 2004, showed the importance of achieving blood pressure control in the fastest possible time and highlighted the differences between therapeutic strategies. The main objective of the VALOR⁵ study was to discover the prevalence of high-risk hypertensives in the population with AHT that is older than 50 years of age, seen in primary and specialised care in our country. The definition of a high-risk hypertensive was established based on risk factors and diseases and was based on the algorithm according to age and gender from the VALUE study (table 2).

The clinical characteristics of these patients, the degree of compliance with therapeutic objectives, the differences between the control group and non-control group, and the prevalence of metabolic syndrome and diabetes were also estimated. It was an epidemiological, cross-sectional, observational, multicentre, nationwide study in which each research physician gathered data from all patients seen in a consecutive manner until reaching the goal of 8 patients who met the inclusion criteria; these criteria included being older than 50 years of age and a mild to moderate level of AHT with or without treatment. Between March and October 2005, 9,533 patients were included, of which 4,627 were women (48.53%). When the classification of high risk was taken into account, 62% of women met the criteria, compared with 74% of men, because in the age range of 50-59 years, women had to present with at least three factors plus one disease or two diseases to be considered high risk [males of this age were considered as high risk with three cardiovascular risk factors (CVRF) or one cardiovascular disease].

KORAL-CARDIO Study. Albuminuria and cardiovascular risk

The detection of albumin in urine should be a part of the risk stratification of patients with AHT and diabetes because a close relationship between the risk of cardiac, vascular, and renal complications has been found. As a result, its reduction or reversal is one of the therapeutic objectives in these patients. Albuminuria allows for the identification of a group of individuals with more advanced diseases, is a marker of organ

damage, forces a stricter control of arterial blood pressure readings, and gives guidance regarding the need to use pharmaceuticals that block the renin-angiotensin system (RAS). These medications have been shown to be associated with greater cardiovascular and renal protection, in particular with diabetics. Existent data indicate that albuminuria is frequent found in patients with cardiovascular diseases, in particular ischemic or hypertensive cardiomyopathy and cerebrovascular diseases, and is associated with a poorer prognosis. The objective of the KORAL-CARDIO⁶ study was to determine the levels of albuminuria and the associated clinical characteristics in a group of hypertensive patients with diverse cardiomyopathies (atrial fibrillation, LVH, or chronic ischemic cardiomyopathy) that were not treated with pharmaceutical inhibitors of RAS as well as to analyse the influence of diabetes mellitus type 2 in these results. The KORAL-CARDIO study was designed as a multicentre, prospective, and observational trial. The period of recruitment began in September 2002 and lasted for 6 months, with an estimated follow-up time of 24 months. Two hundred and fifty-nine cardiologists who had outpatient cardiology consultations distributed throughout the Spanish territory participated in the study, which included consecutive patients who met the specified inclusion criteria: AHT (arterial blood pressure³ 140/90 mmHg with or without treatment) and any of the following concomitant cardiomyopathies: chronic or paroxysmal atrial fibrillation, LVH according to the electrocardiographic criteria, or chronic ischemic cardiomyopathy (angina, acute coronary syndrome without ST elevation, or previous revascularisation), and that also had quantitatively-determined albuminuria. Eleven total of 2,711 patients were included, of which 1,220 were women (45%). When classified according to the presence of diabetes, women reached 46.3% (44% amongst the non-diabetics).

CAROL study. Degree of arterial blood pressure control in high-risk hypertensive patients in cardiology consultations

The significance in controlling arterial blood pressure in high-risk patients is well known, as is the fact that achievement of therapeutic objectives is insufficient in the clinical context. However, regardless of the information on baseline characteristics of patients that the records from the clinical setting provide, they have a marked influence on daily practice, and it is therefore important to repeat the analysis after a given amount of time to establish its effects. The CAROL⁷ study is an epidemiological, prospective, and nationwide multicentre study. The main objective of the study was to determine the degree of arterial blood pressure control in high-risk

hypertensive patients seen in cardiology consults, and the secondary objectives were the following: to study the progression at 3 months after treatment of other risk factors; to calculate the percentage of patients that reached an optimal control of arterial blood pressure; to establish the cardiovascular risk profile of hypertensive patients in cardiology (years of progression, arterial blood pressure values, target organ damage, and associated CVRF); and to identify treatment preferences in cardiology and the guidelines followed in these patients. Six hundred seventy-seven patients were included, of which 42% were women.

REFRACVAS Project. Prevalence of treatment-resistant hypertension in the clinical practice

The data are disparate with respect to the prevalence of resistant arterial hypertension (defined as that which is not controlled despite treatment with three pressure-lowering medications, one of which is a diuretic), depending on the area of study as well as the clinical characteristics of these patients. REFRACVAS is an observational, cross-sectional, multicentre, and non-comparative study conducted in hypertension hospital units and in primary care. The study was designed to elucidate the prevalence and clinical and therapeutic characteristics of patients with resistant AHT in specialised medicine (cardiology and internal medicine) and primary care medicine in Spain. In addition, the study sought to demonstrate if differences in risk factors, history of cardiovascular disease, metabolic syndrome, medications, and being overweight exist between males and females and between patients below or above 55 years of age. Additionally, the study sought to evaluate renal function through the estimation of the glomerular filtrate and the urinary albumin determination. Hypertensive patients that had external consults from the hypertension hospital units and/or primary care consults, up to a maximum of 50 during the 3 months that the study lasted, were included. Data were available for 15,217 patients, of which 40% were women.

ANALYSIS OF RESULTS OF THIS STUDY IN RELATION TO GENDER

From all of the records described, almost 50,000 hypertensive patients were included (48,239), of whom 45.239% were women. When evaluating the differences between genders, results were concordant in various parameters (table 3). The median age for women was greater by approximately 3 years in the most populous age bracket, which was between 60 and 70 years. With respect to weight, the proportion of obese women was greater both in studies, in which data were gathered for the measurement of abdominal obesity and in studies of body mass index (BMI).

TABLE 3. Differences in risk factors, target organ damage, established cardiovascular disease, and its management between men and women included in reports of arterial hypertension

	Women (n = 22,082)	Men (n = 26,157)
Age	+	-
Risk factors		
Obesity	+	-
Diabetes Mellitus	+	-
Smoking	-	+
Hyperlipidemia	+	-
Metabolic syndrome	+	-
Target organ damage		
Left ventricular hypertrophy	-	+
Microalbuminuria	+	-
Serum creatinine	+	-
Cardiovascular disease		
Atrial fibrillation	+	-
Cardiac insufficiency	+	-
Cerebrovascular Disease	+	-
Ischemic cardiomyopathy	-	+
Peripheral artery disease	-	+
Treatment		
Blood pressure values	+	-
Number of anti-hypertensive pharmaceuticals	+	-
Number of pharmaceuticals for comorbidities	+	-

+: greater prevalence; -: lower prevalence.

There were significant differences in most of the CVRFs: the prevalence of diabetes was greater in hypertensive women, and the proportion of smokers was lower in women. Generally, there were also more women diagnosed with hyperlipidemia, but the differences are not always significant. Metabolic syndrome was also found more frequently in women.

Markers of organ damage by AHT, in all records in which the presence of LVH was analysed by EKG, were most frequent in males. When evaluating the renal implications caused by microalbuminuria or increased serum creatinine, greater values were found in women. A greater prevalence of atrial fibrillation, cardiac insufficiency, history of cerebrovascular diseases, and a lower prevalence of ischemic cardiomyopathy and peripheral arterial disease were found in hypertensive women. Lastly, and in relation to treatment, women in general had worse blood pressure control despite receiving more anti-hypertensive medications but also had higher quantities of medications for concomitant diseases that may have a negative influence on pressure control (e.g., anti-inflammatories and anti-depressants).

CLYDIA study. Prevalence of the metabolic syndromes: an epidemiological study in patients with cardiovascular disease

This was a study promoted by the Heart and Diabetes Group, integrated in the Arterial

Hypertension Chapter, to better understand the prevalence of metabolic syndrome (MS) according to ATP-III criteria in populations with established cardiovascular disease (coronary, cerebrovascular, or peripheral arterial disease). The study also had the objective of evaluating the prevalence of each component of MS and the therapeutic management of these patients, including its agreement with the international consensus recommendations⁸. Patients were recruited from cardiology, endocrinology, internal medicine, and primary care services by 100 physicians, resulting in the inclusion of 1,342 patients in the study. Data were available from 1,313 patients for analysis of gender differences, 30.5% of which were women (n = 400). The median patient age was 66 years old for men and 70 years old for women. The ATP-III criteria for the diagnosis of MS were used [i.e., needing to meet three or more of the following criteria: abdominal obesity (abdominal perimeter of > 102 cm in men and > 88 cm in women); triglycerides > 150 mg/dl; high density lipoprotein cholesterol (HDL) < 40 mg/dl in men and < 50 mg/dl in women; systolic arterial pressure³ of 130 mmHg or diastolic³ of 85 mmHg; and a fasting glucose level of > 110 mg/dl].

The prevalence of MS was significantly greater (p < 0.0001) in women than in men (51.5% vs. 31.8%) (fig. 2). Some of the components of MS were also more prevalent in women. Of the 51.5% percent of women diagnosed with MS in the study, 21% met three criteria, 23% met 4 criteria, and 7.5% met five criteria.

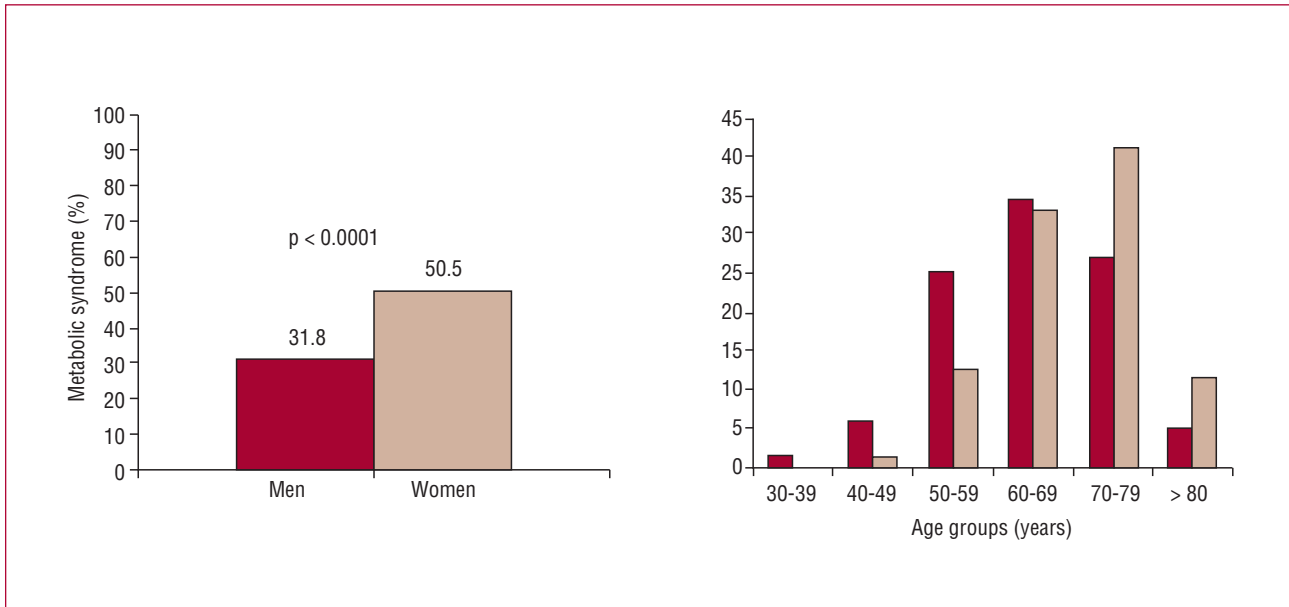


Fig.2. Prevalence of metabolic syndrome according to gender and distribution by age (CLYDIA study).

Of the 31.8% of men, 18.8% met three criteria, 10.2% met 4 criteria, and 2.8% met 5 criteria. Women had a significantly greater prevalence of abdominal obesity and low HDL, while men presented with greater frequency of hypertriglyceridemia, higher arterial pressure, and higher basal fasting blood glucose (> 110 mg/dl). Among patients with MS, women were older than men (median 69.5 years old for women and 64.3 for men) and had a higher BMI (32.2 vs. 31.1), which was statistically significant for both cases. The group of men had significantly more smokers and drinkers and was more physically active. In this census, all patients had an established cardiovascular disease. In those in which MS criteria were met, the proportion of coronary disease was similar between genders (76.2% for men and 71.8% for women), but there were significant differences in the proportion with peripheral arterial disease (22.4% of men vs. 10.2% of women), in prevalence of ischemic cerebrovascular disease (27.2% of women vs. 19% of men), and cardiac insufficiency (20.4% of women vs. 13.4% of men).

Among CVRFs, diabetes (70.9% vs. 64.8%, $p < 0.0001$), AHT (92.2% in women and 79.2% in men; not significant) and low HDL (76 in women and 53.4 in men; $p < 0.0001$) were found more frequently in women. In contrast, smoking was more frequent in men (44.5% in men and 4.9% in women; $p < 0.0001$). There was a greater proportion of underlying risk factors in women, which were defined according to ATP-III: abdominal obesity (96.6% of women and 80% of men; $p < 0.0001$) and sedentary lifestyle (39.3% vs. 25.9%; $p < 0.002$). The total cardiovascular

risk for having a cardiovascular event during the next 10 years, according to the Framingham equation, was greater for men in this study in both those with and without MS (compared with women with or without MS). No differences were found in the pharmacological treatments, although there was a tendency in women to receive more concomitant treatments.

PAMISCA study. Peripheral arterial disease prevalence in patients admitted for acute coronary syndrome (ACS)

This study included 1,406 patients admitted for ACS between September and November 2005. The distribution by gender was 1,003 men and 403 women⁹. The age of women was significantly higher than that of men (70 years vs. 64 years). As in the previous census, the prevalence of obesity, AHT, and diabetes was greater in women, and smoking was greater in men. There were no differences in the proportion of patients with hyperlipidemia. There was also no difference between genders regarding a history of cardiovascular disease, except that women had a higher occurrence of cardiac insufficiency (11.9% vs. 6.7%), and more men had a diagnosis of peripheral arterial disease (19.3% vs. 12.4%). The ankle-arm indices (AAI) were similar for both males and females.

With respect to target organ damage, a higher proportion of moderate and severe renal insufficiency was detected in women when calculating creatinine clearance. The type of ACS also differed with ST

TABLE 4. Relationship between risk factors and the presence of peripheral artery disease in the PAMISCA study

	OR	CI of 95%	p
Age	1.05	1.04-1.06	< 0.0001
Gender	1.09	0.81-1.47	0.56
Arterial Hypertension	1.34	0.98-1.82	0.059
Smoker	2.22	1.57-3.13	< 0.0001
Diabetes Mellitus	1.38	1.09-1.77	< 0.01
Hypercholesterolemia	1.46	1.05-2.03	< 0.05

elevation ACS (ST-ACS) being more frequent in men and non-ST elevation ACS (NST-ACS) more frequent in women. There were no statistically significant differences in left ventricular ejection fraction. Coronary angiography was performed in 67.3% of men and only 40.5% of women (p < 0.0001). A higher proportion of one vessel disease was found in men and of three-vessel disease in women. Coronary revascularisation was performed with higher frequency in men (60.2%) than in women (43.1%) (p < 0.0001). In patients with ST-ACS, fibrinolysis was performed in 18.7% of men and only 11.1% of women (p = 0.0006). As shown in table 4, gender was not an independent predictor of peripheral artery disease in the multivariate study.

With respect to pharmacological treatment (fig. 3), a lower proportion of women received anti-platelet aggregation, both acetylsalicylic acid (ASA) as well as

clopidogrel (although during admission, more women received glycoprotein IIb/IIIa inhibitors) and statins (79% vs. 83%) and received oral anticoagulants (10 vs. 5%), fibrates (2.7 vs. 1.2%), oral nitrates (42.8 vs. 31.2%), diuretics (31.4 vs. 16.3%), ARB-II (18.8 vs. 10.2%), and anti-diabetics in higher proportion than did men. There were no differences in the prescription of other cardiovascular pharmaceuticals (ACE inhibitors, beta blockers, calcium antagonists, and peripheral vasodilators).

CONCLUSIONS

The data presented in this report are, from our point of view, of great clinical and epidemiological interest because they analyse the gender differences in more than 50,000 hypertensive patients, of which 45% are women, in different settings of the cardiovascular disease continuum. Although the conducted studies had different objectives and designs, they have great similarities as a whole, and their results are comparable from the clinical point of view.

From the general analysis, we can conclude that women included in the various studies had a worse risk profile than men did. In addition, there were differences in the diagnostic and therapeutic focus that could at least partly justify the worse cardiovascular disease prognosis in women. All of these data may serve as the foundation for the development of programs or specific actions to correct this situation.

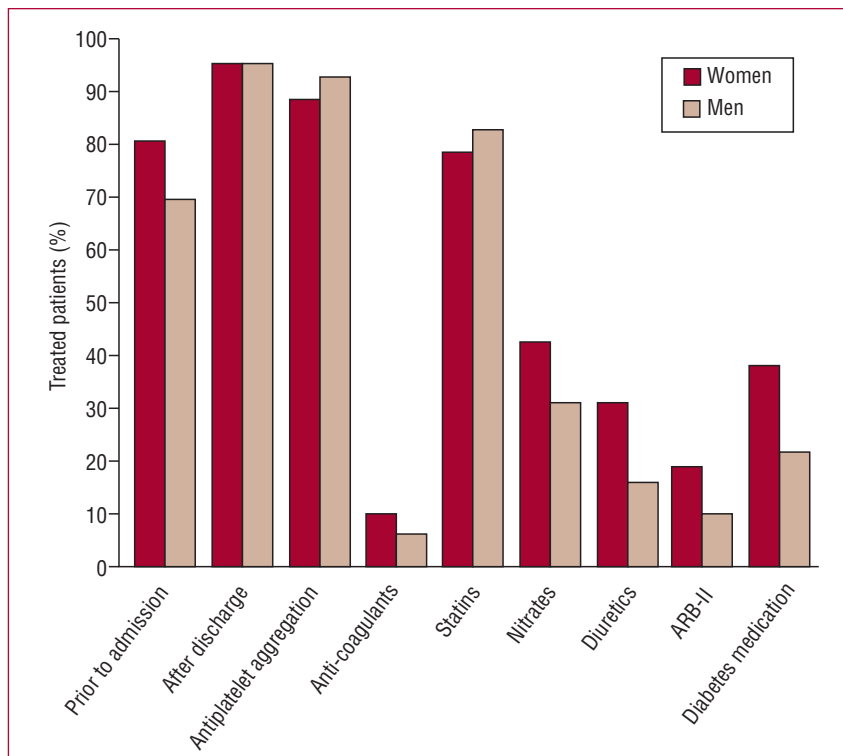


Fig. 3. Pharmacological treatment (%) prior to admission and after discharge of patients in the PAMISCA study. Differences according to gender.

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Atrial Fibrillation in Women: An Analysis of the Situation in Spain

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Atrial fibrillation is the most common sustained arrhythmia observed in the general population. It has a substantial impact on morbidity and mortality in elderly individuals. Most data on the epidemiology of atrial fibrillation come from the United States, in particular from the Framingham study. No comprehensive data are available for Spain. However, some studies have found prevalence rates of between 2% and 17% in the country, depending on the age group included and the scope of the study. In addition, some of these studies indicate that the prevalence in men and women is different, but no reliable data are available for Spain. Given the increasing importance of this arrhythmia and its impact on prognosis, it would be advisable to carry out specially designed studies to improve our understanding of the current situation in Spain, both in general and in the individual sexes.

Key words: Atrial fibrillation. Sex differences. Prevalence.

Fibrilación auricular en la mujer: análisis de la situación en España

La fibrilación auricular es la arritmia sostenida más frecuente en la población general y tiene un gran impacto en la morbimortalidad de personas de edad avanzada. La mayor parte de los datos sobre epidemiología de la fibrilación auricular procede de poblaciones norteamericanas, especialmente del estudio de Framingham, y no hay datos generales en España. Algunos estudios encuentran cifras de prevalencia de fibrilación auricular en España entre el 2 y el 17%, dependiendo de la edad y el ámbito de estudio. En algunos de ellos se señalan también las distintas prevalencias en mujeres y varones, pero no existen datos fiables sobre este aspecto en nuestro país. Dada la importancia creciente de esta arritmia y sus repercusiones pronósticas, parece necesario realizar estudios específicamente dirigidos a conocer su situación real en España, tanto en general como diferenciada por sexos.

Palabras clave: Fibrilación auricular. Diferencias de sexo. Prevalencia.

INTRODUCTION

Atrial Fibrillation (AF) is the most frequent arrhythmia suffered by the general population. It causes a great number of hospital admissions for its symptoms, tachycardia (palpitations, dizziness, or syncope), or its consequences. Today we know that the AF per se increases the patient's mortality as it multiplies the risk of death by factors of 1.5 in men and 1.9 in women¹. The bulk of the data published regarding the prevalence of AF comes from the American population, especially the Framingham study², although similar results have been recently

published in Europe^{3,4}. The data from this study have demonstrated a prevalence of AF in 4/1,000 inhabitants in the general population (0.4%). These numbers are much higher in the elderly population as AF affects almost 10% of people over 80 years old.

ATRIAL FIBRILLATION PREVALENCE IN SPAIN

In Spain, we have no sufficiently broad studies to ascertain the prevalence rates of AF in the population. Only a small number of studies have been performed and published within the past few years, and most of them have a retrospective or transversal design⁵⁻¹⁰ (table 1).

The REGICOR study rated the AF prevalence secondarily in a random sample of 1,748 individuals, ages 25 to 74, from the city of Girona. The data in this population are similar to that from other industrialised countries, but the main limitation of the study resides

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TABLE 1. Studies about atrial fibrillation prevalence in Spain

Study	Design	Field	Prevalence (%) Men/women/total
Candel ⁵	Retrospective	FC	2.47/2.55/2.52
CARDIOTENS ⁶			
FC		FC	2.49/2.94/2.75
SC		SC	16.6/18.7/17.6
REGICOR ⁷	Transversal	AF permanent, 35-75 years	1.1/0.3/0.7
Barbanza ⁸	Transversal	FC	—/—/4
Vázquez ⁹	Transversal	FC	—/—/11.5
GEFAUR I ¹⁰	Transversal	Emergencies	—/—/3.5

AF: atrial fibrillation; FC: first care; SC: specialised care.

in the low absolute number of AF patients found and the exclusion of the population above 74 years old, where we know there is a higher prevalence of cases. In another study of 1,206 people above 65 years old in a healthy area of Toledo, an AF prevalence of 5.6% was observed (3.9% up to 74 years old, 8% between 75 and 84 years old, and 18.2% above 85 years old). In this study, the prevalence in women was of 6.4% versus 5.6% in men, which contrasts with the higher number of men in the Framingham and REGICOR studies⁷. In Spain, among the patients that go to cardiology appointments for the first time, AF is the most frequently discovered arrhythmia (11.5%), followed by paroxysmal supraventricular tachycardia (2.1%), and the atrial flutter (0.8%)⁹. There are no data revealing the actual AF prevalence in the elderly population of our country, and the current discrepancies in the data exist because the studied populations are very different. Nevertheless, using available numbers, we can say that there are almost 100,000 new cases of AF in Spain each year.

As was already discussed, age is directly related to the frequency of AF occurrences, which can affect around 10% of people older than 80 years old. In this sense, in our society, it has been estimated that 4 in 10 patients with AF are above 70 years old⁶. Even though the risk of AF is higher in men than in women in almost all age groups, the total number of cases tends to be same due to longer survival of women.

The European Society of Cardiology has recently published data in a study about the characteristics of 5,333 AF patients from 35 European countries. Spain provided data for 848 patients, mainly from cardiology appointments.⁴ Following the classifications suggested above, the data showed that when an AF diagnosis was given, 20% of the patients were diagnosed with an arrhythmia for the first time (with undetermined evolution time in most cases), 18% of patients had already diagnosed paroxysmal AF, 20% had persistent AF, and 42% had permanent AF (fig. 1). More than 50% of the patients also had hypertension, and heart failure was observed in a subset of patients, from 20%

in the paroxysmal AF group to more than 40% in the permanent AF group (fig. 2). The percentage of women in each group was similar, at about 40%.

ATRIAL FIBRILLATION AND ANTICOAGULATION

The indication of chronic oral anticoagulation and the risk factor for clots in patients with AF is well established and corroborated by the Spanish and American action guides¹¹. As part of the European study, it was observed that about 80% of all the patients seen in Spain had a high risk of clots. Despite that finding, anticoagulant treatment had failed to be recommended to an important percentage of patients who did not have any contraindications for such treatment. This finding is more common in elderly patients and women. In patients with AF who were admitted after a cerebrovascular accident (CVA), previous anticoagulant treatment could diminish the severity of the CVA embolism, which means that even in cases of failed stroke prevention, the antithrombotic treatment could provide partial protection.

It is known that long-term morbid-mortality effects from AF vary widely by gender. In a prospective study with individuals between 45 and 65 years old, AF was associated with an 89% probability of a cardiovascular event in women during the following 20 years compared with 27% in men. In women, 27% of strokes are considered directly related to AF, versus only 11% in men. Until the year 2005, information regarding a variable risk of stroke embolism due to gender was controversial. However, in some studies (SPAF, Framingham), females presented with higher risks of stroke, while in others (AFI, index CHADS¹²), no differences were observed. In 2005, the ATRIA study was published with about 13,559 AF patients, specifically focused in detecting those differences^{13,14}. This study concluded that women with AF have, in the absence of anticoagulation therapy, a higher risk of stroke compared to men (3.5% versus 1.8%, respectively) in all age groups. Additionally, the study

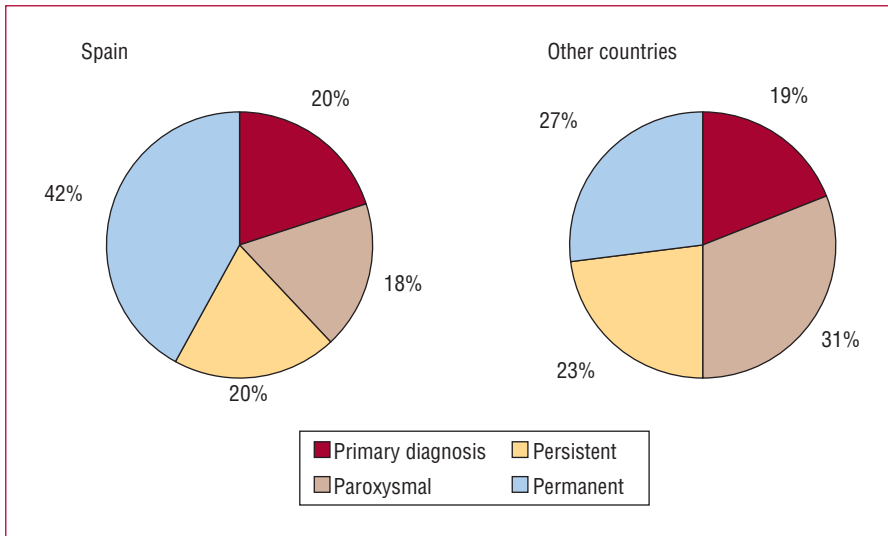


Fig. 1. Type of atrial fibrillation observed at the time of diagnosis (taken from EuroSurvey Spain. Data provided by Dr. V. Bertomeu).

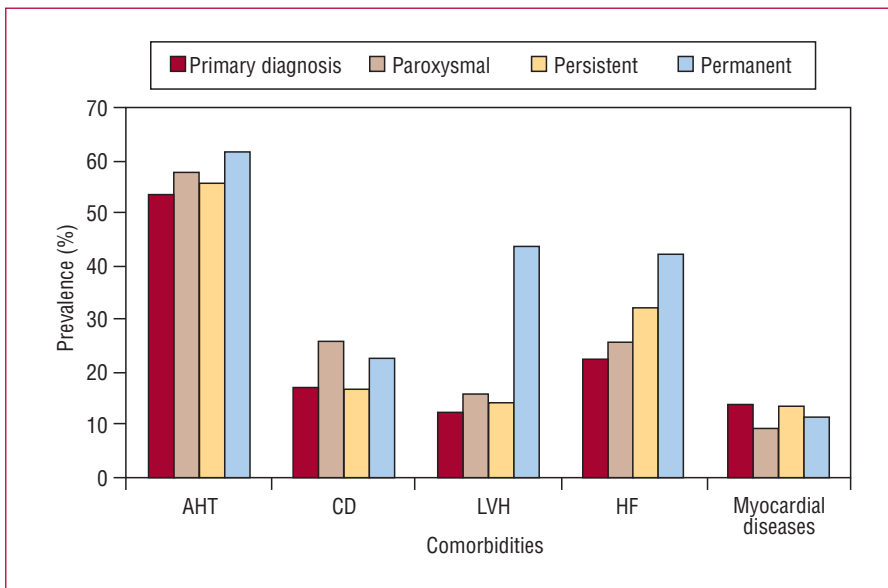


Fig. 2. Atrial fibrillation comorbidities. AHT: arterial hypertension; CD: coronary disease; HF: heart failure; LVH: left ventricular hypertrophy (taken from EuroSurvey Spain. Data provided by Dr. V. Bertomeu).

states that oral coagulation with warfarin is at least as effective, if not more so, in women versus men. No one knows the cause for the higher prevalence of embolic accidents in women with AF. The last fact contrasts the policy, which is unfortunately very commonly applied, that does not suggest anticoagulant treatment to women over 75 years old, even though studies indicate that this demographic group has a higher risk of stroke. Furthermore, other studies have shown that women present with a less favourable clinical course including significant differences regarding the clinical severity of CVA, intra-hospital mortality, and disabling sequelae. In the CARDIOTENS⁶ study performed in Spain, low percentages of anticoagulation therapy were observed (26% of patients at first care and 41% of patients in

cardiology appointments), and the proportion of patients treated with anticoagulation is reduced with age (only 26% of the patients over 80 years versus 50% below 65 years, among those treated by cardiologists).

CONCLUSIONS

There are no studies from which one can extract reliable data on the differential AF characteristics in men and women in Spain. Some studies show quite variable numbers of prevalence depending on the age of the studied populations, the design, and field where they were performed (e.g., general population or emergency treatment records, in primary care, or associated with cardiologist treatments). There are also

no longitudinal studies that indicate the impact of this arrhythmia, its management, or the long-term prognosis. Therefore, given the growing importance of AF, it seems essential to design and conduct studies throughout the country that provide us with valid and reliable information on all of these issues.

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Valvular Heart Disease in Women: Sex Differences in Spain

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Although the prevalence of valvular heart disease is lower than that of other cardiovascular diseases, patients with the condition require a significant amount of care and place a burden on healthcare resources. No studies specifically designed to investigate possible sex differences in the characteristics of valvular heart disease have been carried out in Spain. The only studies that have provided relevant information are a number of limited observational studies, which were mainly carried out in Andalusia. These studies indicate that sex differences in the etiology and treatment of these conditions could exist. Specially designed studies are required to clarify the situation.

Key words: *Valvular heart disease. Sex differences. Etiology.*

Valvulopatías en la mujer: diferencias de sexo en España

Las valvulopatías, aunque su prevalencia actual es menor que la de otras enfermedades cardiovasculares, siguen siendo una causa importante de necesidad de asistencia y consumo de recursos en nuestro entorno. No existen en nuestro país trabajos que hayan evaluado de forma específica si hay diferencias relacionadas con el sexo en las características de las enfermedades valvulares. Sólo registros parciales, realizados sobre todo en Andalucía, ofrecen algunos datos sobre estos aspectos e indican que puede haber diferencias relacionadas con el sexo en el perfil etiológico y en el manejo de estas lesiones. Son necesarios estudios específicos y diseñados para proporcionar respuestas sobre estos aspectos.

Palabras clave: *Valvulopatías. Diferencias de sexo. Etiología.*

INTRODUCTION

Despite being less common than other cardiovascular diseases, such as heart failure or ischemic cardiomyopathy, valvulopathies remain a major underlying cause of requests for medical assistance and a drain on medical resources in Spain. However, little information is available as to the actual prevalence and clinical profile of the disease in the country as a whole; the numbers that are available come from surgical records¹⁻⁴ or global sources such as European records⁵, which may not be representative of the local geographic and social environment. Furthermore, there have been no studies investigating the prevalence of valvulopathies in Spain.

On the other hand, in recent years, heart valve disease has become a dynamic and evolving problem as a result of several factors that include an increase in the incidence of degenerative valvulopathies due to an

increase in the mean age of the Spanish population that has resulted in significant comorbidities, and the eradication of rheumatic fever in Spain a few decades ago. Nevertheless, the sudden demographic changes that have been taking place over the last few years, with the influx of an immigrant population, have resulted in an increase in the number of cases in young patients, among them pregnant women; a situation that was rarely seen in the prior two decades. Furthermore, if one wanted to examine gender differences with respect to valvulopathies, one would find that there is even less information available. Even the most important study on the profile of valvulopathies in the country, the Euro Heart Survey on Valvulopathies, refers to gender only twice. In this study, we review the limited information available on gender differences in the diagnosis and treatment of valvulopathies in our country.

AVAILABLE STUDIES

Euro Heart Survey on Valvular Heart Disease

This study was designed to identify the characteristics, treatments and evolution of patients

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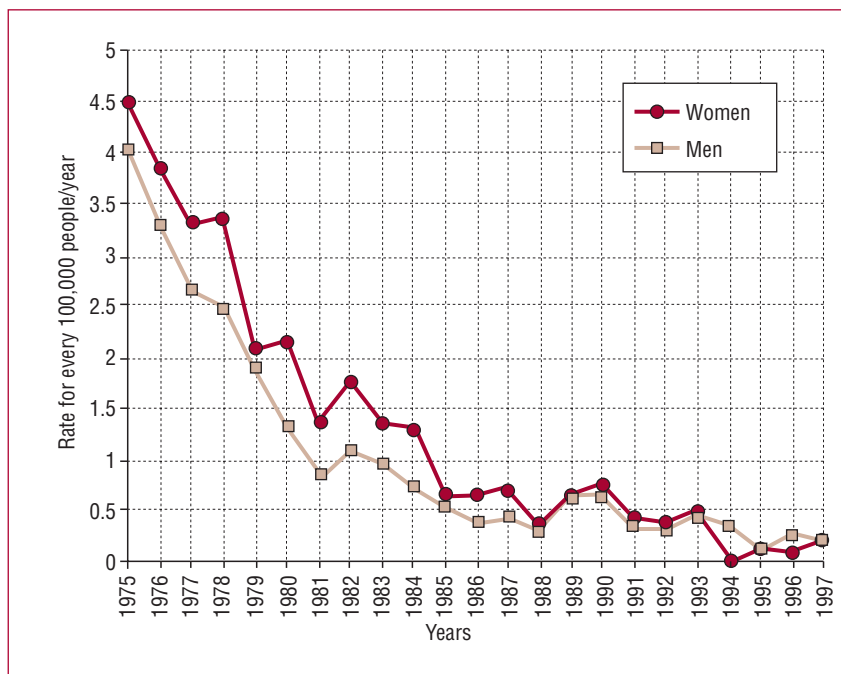


Fig. 1. Evolution of the standardized death rate due to chronic rheumatic heart disease. Andalusia, 1975-1997.

with valvulopathies in Europe. It was conducted from April to June of 2001 across 922 centres in 25 countries, and it included 5,001 adults with moderate or severe valvular heart disease, endocarditis or a previous valve intervention. Of the patients studied, 49.5% were women. Nevertheless, no specific analysis was conducted as to the role of gender on the aetiology, diagnosis or treatment of the disease. The only reference to gender was that 46.7% of the patients that had undergone a valvular intervention were women. Spain was an active participant of this survey, contributing 609 patients, yet no information is available as to the gender of the patients.

Andalusian Statistics Institute

The data derived from the mortality statistics in Spain may be unreliable due to a variety of reasons, from the irregularity and lack of precision in death certificates to the nomenclature sometimes used to classify them. Nevertheless, these data can provide an unclear yet fairly representative overview of the situation. From this information, we can confirm a well known fact, which is the absence of rheumatic fever, and thus, a decrease in the number of deaths due to rheumatic valvulopathies. This decrease is identical for both men and women (fig. 1). From further analysis of this data, specifically looking at the year 2000, we can observe that the main cause of death due to valvulopathies was non-rheumatic aortic valvulopathy, with a slightly higher incidence in women than men, especially for patients over 75 years of age. The incidence of non-rheumatic mitral

valvulopathies was higher in women across all age groups (fig. 2).

Andalusian registry of valvulopathies

The Andalusian registry of valvulopathies collected patient data for all hospital admissions as a result of problems directly related with severe valvulopathy in the years 2001, 2002, and 2004 across eight Andalusian hospitals⁶. The general characteristics of the patients are shown in tables 1 and 2 for each year. There are 733 patients in the registry, of which 655 can be analysed according to their gender. Despite being only limited to three years where, in fact, only the last trimester of 2001 is available, the data

TABLE 1. General characteristics of patients with valvulopathies (Andalusian registry of valvulopathies 2001-2004)

	2004 (n = 287)	2002 (n = 368)	2001 (n = 78)
Age (years)	69.3 ± 12	67.6 ± 12	69.1 ± 16
Men	40.8	47.6	52.1
Rheumatic fever	22.6	20.7	23.3
Ischemic cardiopathy	10.3	5.7	16.4
Previous valve intervention	12.9	14.4	9.6
Hypertension	53.3	39.7	45.2
Diabetes mellitus	27.9	24.7	19.2
Dyslipidemia	24.0	15.2	15.1
Smoking	16.0	15.5	19.2

Data are either percentage or mean ± standard deviation.

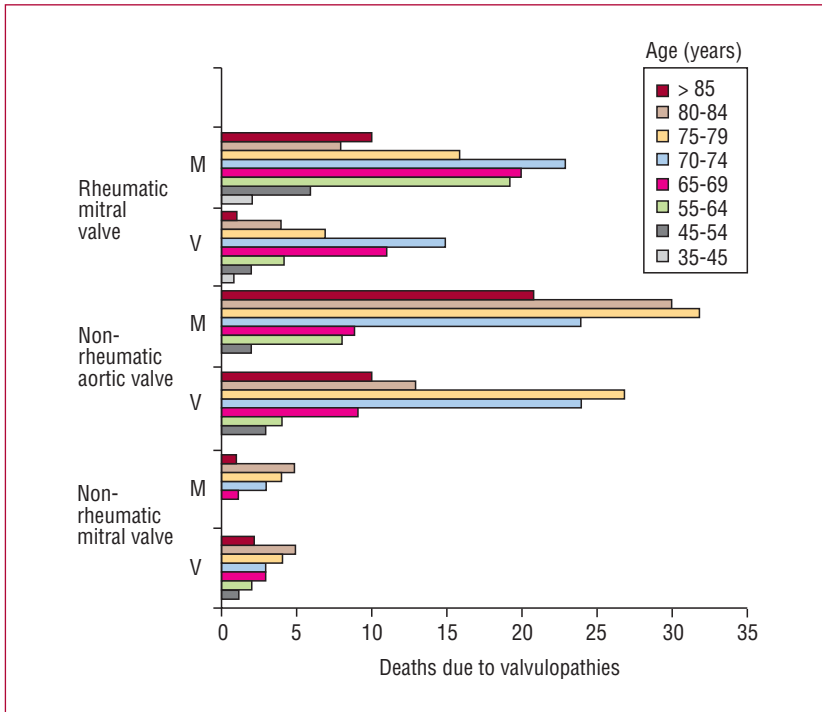


Fig. 2. Death rate due to valvulopathies for different age groups. Andalucía, 1975-1997. M: men; W: women.

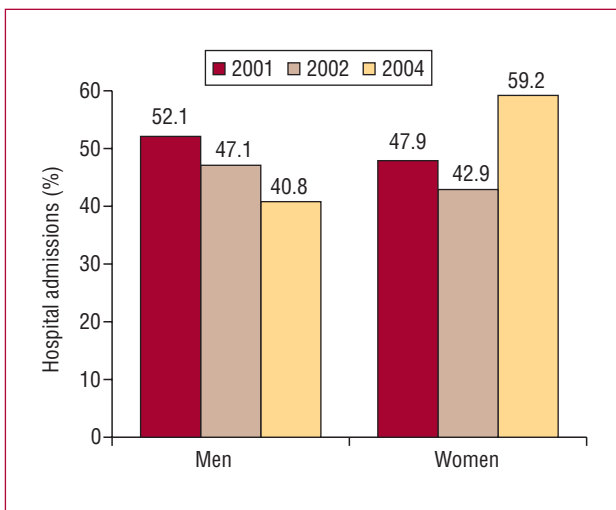


Fig. 3. Percentage of hospital admissions due to significant valvulopathies for each gender in the Andalusian registry of valvulopathies.

illustrate a rising trend in the percentage of women with severe valve disease that were admitted to hospitals during that time (fig. 3).

There are no gender differences with respect to the reasons for hospital admittance, although there was a non-significant trend suggesting a higher incidence of heart failure in women and angina in men (figs. 4 and 5). The women with severe valvulopathy present haemopathies (mostly anaemia) at a higher frequency compared to men; whereas in men, concomitant pneumopathies (COPD) were three times more

TABLE 2. General characteristics of patients with valvulopathies in the Andalusian registry of valvulopathies according to gender

	Men (n = 291)	Women (n = 364)	p
Age (years)	67.8 ± 11	68.0 ± 12	
Rheumatic fever	12.3	28.9	< 0.05
Ischemic cardiopathy	11.5	9.5	
Previous valve intervention	12.0	15.2	
Hypertension	42.8	47.9	
Diabetes mellitus	22.3	29.2	
Dyslipidemia	17.5	20.4	
Smoking	26.4	7.2	< 0.05

Data are either percentage or mean ± standard deviation.

frequent than in women. Men also had a higher tendency to suffer from renal failure, but not to a statistically significant degree (fig. 6).

In the Andalusian registry, the doctors that treated the patients also assigned the aetiology based on the clinical criteria used to discharge the patient. When evaluating the causes of severe valve disease and segregating them by gender, rheumatic aetiology was the predominant cause in women (32.3% of women, 14.4% of men). Although degenerative causes were the most frequent in women (44.6%), they actually occur at a slightly lower proportion than in men. The remaining aetiologies (ischemic, congenital, and so on.) tended to be more frequent in men, but not to a significant degree (fig.7). This etiological profile

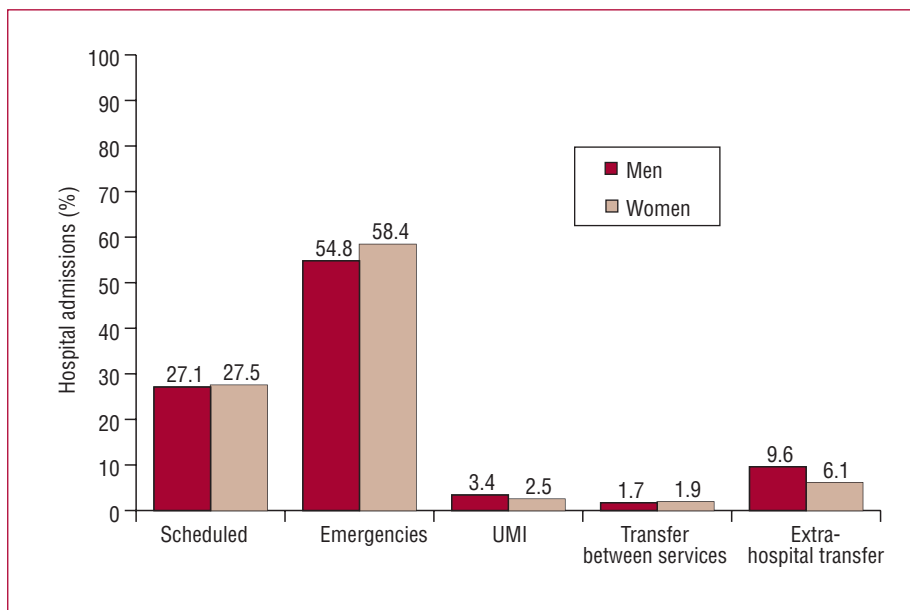


Fig. 4. Source of admitted patients. Andalusian registry of valvulopathies.

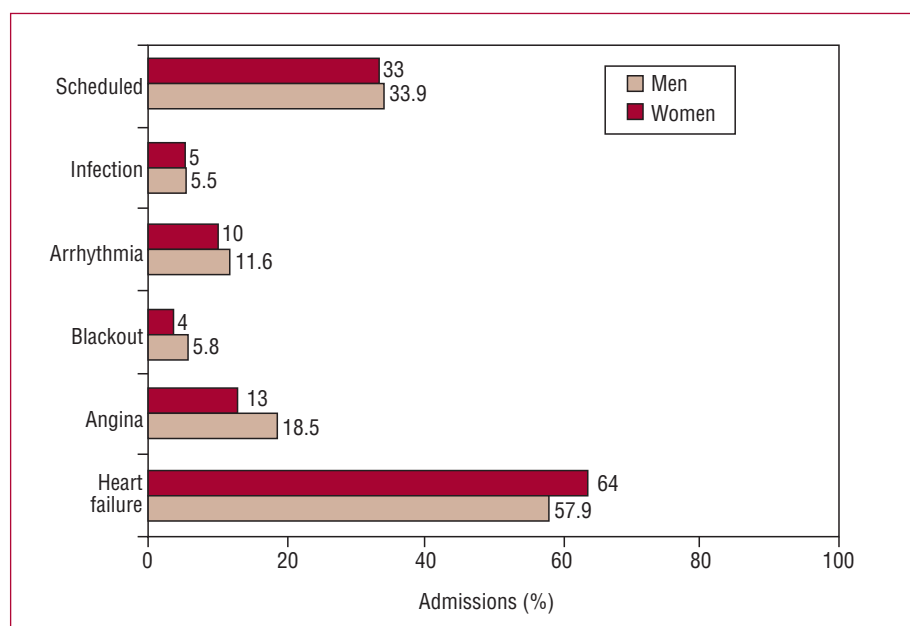


Fig. 5. Reason for admission. Andalusian registry of valvulopathies. This excludes angina and heart failure in women.

shows that most women suffer from mitral stenosis (of rheumatic origin) and tricuspid problems (both stenosis and regurgitation). It should be noted that aortic valve regurgitation was more frequent than stenosis (fig. 8). In view of the etiological distribution of valvulopathies in women, it follows that there is a higher proportion of moderate or severe ventricular dysfunction in men (fig. 9).

Using the data from this registry, we also analyzed the implementation of procedures and therapeutic options with respect to gender. There were no

differences in the usage of the echocardiogram, but differences were found in the implementation of coronarographies. This is related to the higher incidence of ischemic cardiomyopathy and cardiovascular risk factors in men, which makes pre-surgical coronary evaluation necessary. More valvuloplasties are performed in women, but there are no noticeable differences with respect to the implementation of valve replacement surgeries. It is striking that the reason for discharging women has a greater correlation to clinical improvement (45% in

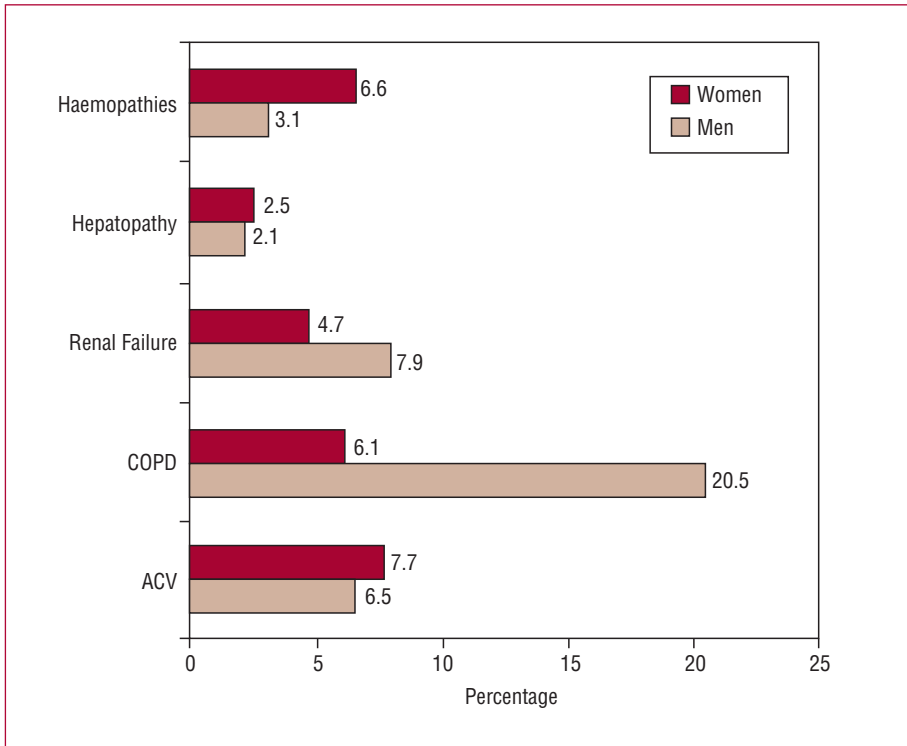


Fig. 6. Comorbidities depending on the gender of the patients (Andalusian registry of valvulopathies).

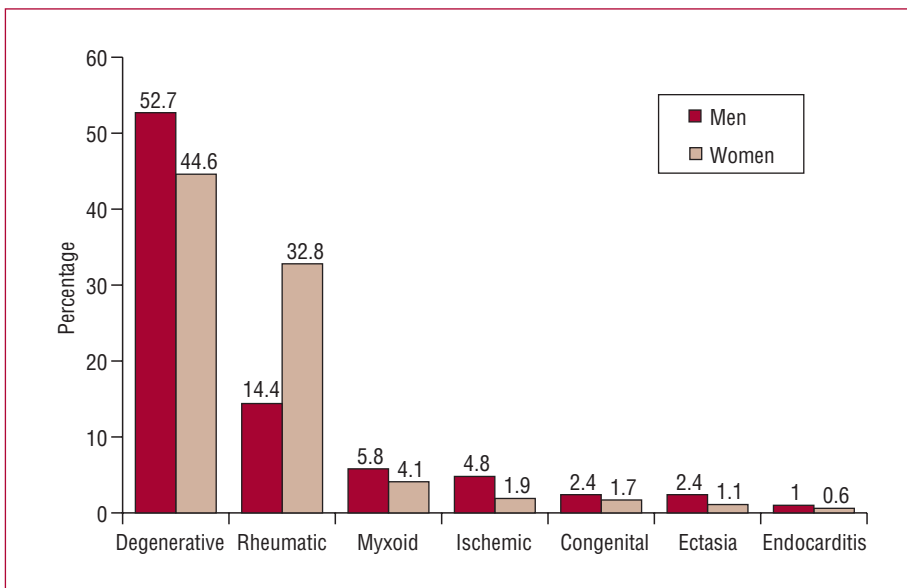


Fig. 7. Aetiology of valvulopathies according to gender (Andalusian registry of valvulopathies).

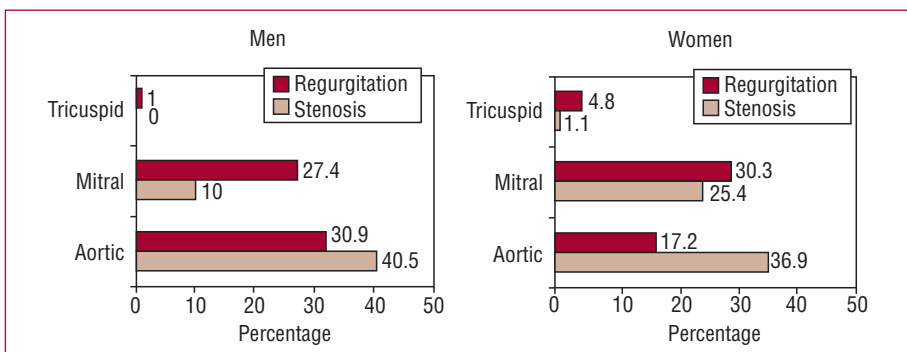


Fig. 8. Affected valve for each gender (Andalusian registry of valvulopathies).

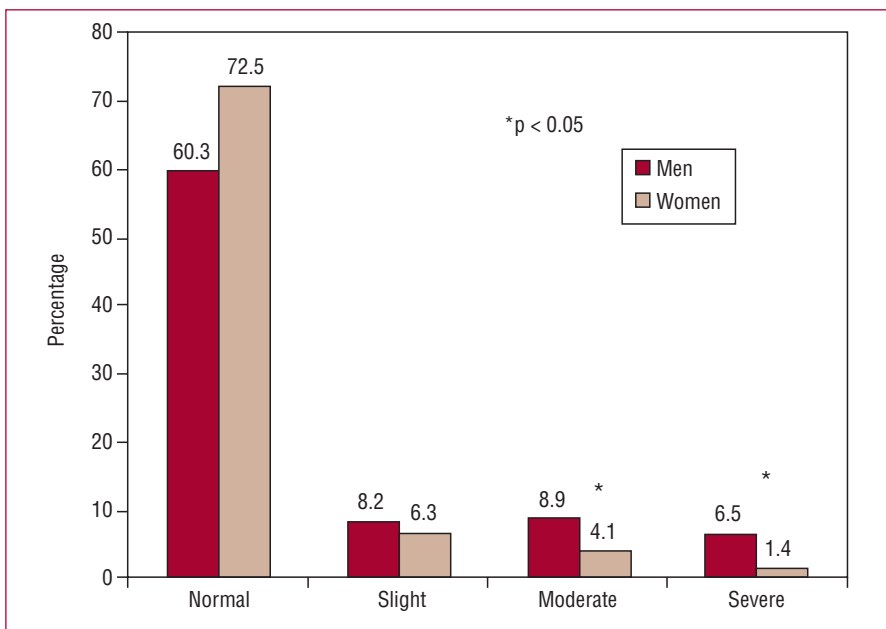
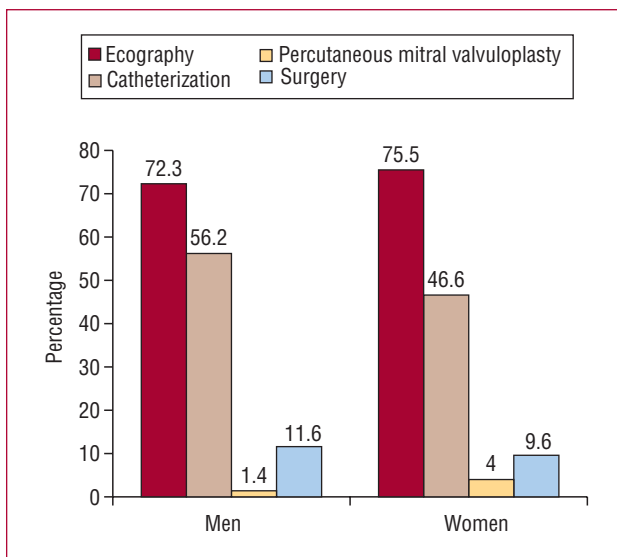


Fig. 9. Level of left ventricular systolic function for each gender (Andalusian registry of valvulopathies).



women vs. 35.2% in men) and a more conservative approach in general (figs. 10 and 11).

CONCLUSIONS

The limited data available in Spain suggest a differential profile of the aetiology of valvulopathies depending on gender, with the rheumatic aetiology being the predominant cause among women and ischemic or congenital being more common in men. The frequency of the degenerative aetiology did not differ between women and men. The lack of reliable and up-to-date references regarding the spectrum of

Fig. 10. Treatments and explorations undertaken in valve disease patients from the Andalusian registry of valvulopathies according to gender.

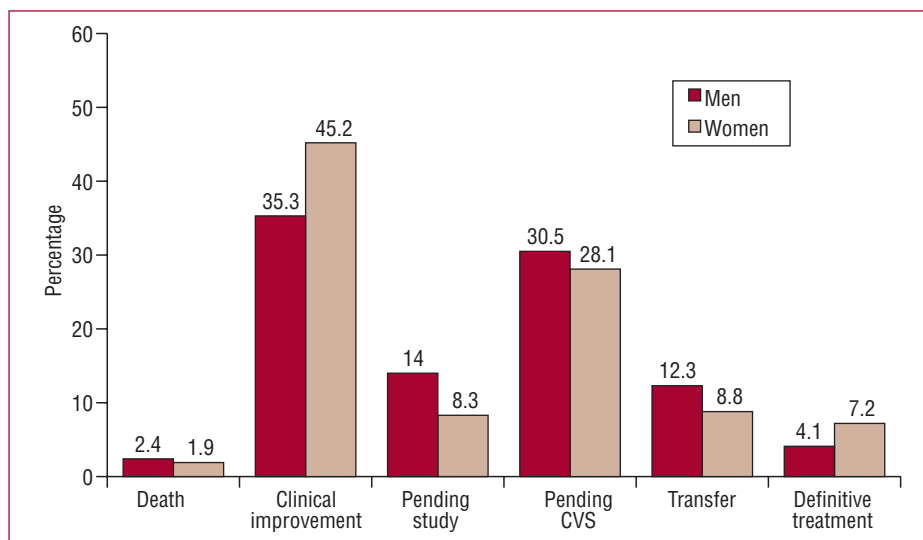


Fig. 11. Final outcome of admitted patients (Andalusian registry of valvulopathies). CVS: cardiovascular surgery.

valvulopathies, particularly with respect to whether there are differences in the etiological profile, diagnosis and handling of these diseases between male and female patients, highlights the need for the design of a new study in Spain to gather such information.

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Influence of Sex on Heart Transplantation Mortality: Data From the Spanish National Heart Transplantation Registry

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The incidence of many heart diseases differs between men and women. In addition, the disease course, the number and type of complications and the prognosis can also be very different. The objective of this study was to determine whether sex differences can be observed in heart transplantations performed in Spain. Outcomes in 762 women who underwent heart transplantations in the country between May 1984 and December 2005 were compared with those in 3646 men. The analysis looked at 100 variables, including characteristics of the recipient, the donor, surgery, immunosuppression and the complications occurring during follow-up. The two sexes were compared using univariate and survival analysis. In addition, multivariate analysis was performed for each sex individually. The ratio of men to women who underwent transplantation was 5:1. Typically, women were younger than men (45 ± 18 years vs. 51 ± 14 years; $P < .05$), had a higher incidence of idiopathic dilated cardiomyopathy (39.8% vs. 31.3%; $P < .05$) and had fewer cardiovascular risk factors (hypertension 16.2% vs. 23.1%; $P < .05$, and dyslipidemia 25% vs. 36%; $P < .05$). Women had more emergency transplants (26.8% vs. 23.4%; $P < .05$) and developed acute graft failure more frequently (17.4% vs. 13.5%; $P < .05$). During follow-up, women had a higher incidence of bone complications (15.5% vs. 10.9%; $P < .05$) and lower incidences of dyslipidemia (38% vs. 45%; $P < .05$), hypertension (36% vs. 49%; $P < .05$), gastrointestinal complications (12% vs. 16%; $P < .05$) and malignancy (9% vs. 12.5%; $P < .05$). The probability of survival was lower in the short term ($P < .05$), but similar to that in men in the medium and long term ($P = 6$). Multivariate analysis identified 14 variables associated with mortality in men, compared with only five in women. In conclusion, important differences were found between men and women who underwent heart transplantation in Spain, but the probability of survival was similar in the two sexes, except in the early stages.

Key words: *Heart transplantation. Sex differences. Mortality.*

Influencia del sexo en la mortalidad por trasplante cardíaco: subanálisis del Registro Español de Trasplante Cardíaco

Muchas enfermedades cardíacas presentan distinta incidencia según el sexo del paciente. También la evolución, el número y el tipo de complicaciones y el pronóstico pueden ser muy distintos. El objetivo de este estudio fue analizar si hay diferencias por sexo en los trasplantes cardíacos realizados en España. Se comparó a 762 mujeres con 3.646 varones trasplantados en España desde mayo de 1984 a diciembre de 2005. Se analizaron 100 variables que incluían características del receptor y del donante, quirúrgicas, inmunosupresión y complicaciones del seguimiento. Se comparó por sexos mediante un análisis univariable y de supervivencia. Se realizó un análisis multivariable de cada sexo. La relación varones:mujeres trasplantados fue 5:1. Las mujeres suelen ser más jóvenes (45 ± 18 frente a 51 ± 14 años; $p < 0,05$), con mayor incidencia de miocardiopatía dilatada idiopática (el 39,8 frente al 31,3%; $p < 0,05$) y menos factores de riesgo cardiovascular (hipertensión, el 16,2 frente al 23,1%; $p < 0,05$; dislipemia, el 25 frente al 36%; $p < 0,05$). Las mujeres se trasplantan más en situación urgente (el 26,8 frente al 23,4%; $p < 0,05$) y desarrollan fallo agudo del injerto con más frecuencia (el 17,4 frente al 13,5%; $p < 0,05$). Durante el seguimiento presentan mayor incidencia de complicaciones óseas (el 15,5 frente al 10,9%; $p < 0,05$) y menor de dislipemia (el 38 frente al 45%; $p < 0,05$), hipertensión (el 36 frente al 49%; $p < 0,05$), complicaciones digestivas (el 12 frente al 16%; $p < 0,05$) y tumores (el 9 frente al 12,5%; $p < 0,05$). La probabilidad de supervivencia fue menor a corto plazo ($p < 0,05$), pero similar a la del varón a medio y largo plazo ($p = 0,6$). El análisis multivariable mostró 14 variables relacionadas con mortalidad en el varón, por tan sólo 5 en la mujer. En conclusión, hay diferencias importantes entre los varones y las mujeres que se trasplantan en España, pero la probabilidad de supervivencia, a excepción de la etapa precoz, es similar en ambos sexos.

Palabras clave: *Trasplante cardíaco. Diferencias de sexo. Mortalidad.*

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TABLE 1. Participants

Hospital de la Santa Creu i de Sant Pau, Barcelona
Universitaria de Navarra Clinic, Pamplona
Puerta de Hierro Clinic, Madrid
Marques de Valdecilla Hospital, Santander
Reina Sofia Hospital, Cordoba
La Fe Hospital, Valencia
Gregorio Marañon Hospital, Madrid
Jimenez Diaz Fundation, Madrid
Virgen del Rocio Hospital, Sevilla
12 de Octubre Hospital, Madrid
Juan Canalejo Hospital. La Coruña
De Bellvitge Hospital, L'Hospitalet
La Paz Hospital, Madrid
Central de Asturias Hospital, Oviedo
Clinic Hospital, Barcelona
Virgen de la Arrixaca Hospital, Murcia
Miguel Servet Hospital, Zaragoza
Clinic Hospital, Valladolid

TABLE 2. Univariate analysis of recipient characteristics

Variables	Women	Men
Age (years old)*	45 ± 18	51 ± 14
Underlying disease		
Ischemic heart disease	19.9	47.5
Idiopathic dilated cardiomyopathy	39.8	31.3
Valvulopathy	11.8	8.6
Other diagnosis	28.5	12.6
Functional status (New York Heart Association)		
III or less	43.5	43.9
IV	56.5	56.1
Body mass index*	23.3 ± 5.4	25.1 ± 4.1
Intravenous inotropes	37.5	34.4
Pulmonary shunt resistors (UW)	2.44 ± 1.74	2.31 ± 1.53
Hypertransaminasemia	23.4	22.6
Insulin dependent diabetes mellitus	11.1	12.9
Hypertension*	16.2	23.1
Dyslipidaemia*	25	36
Previous cardiovascular surgery	26.7	27.1
Automatic Implantable Device*	4.6	7.5

Values are expressed as mean ± standard deviation or as percentages.

*p < 0,05.

INTRODUCTION

It is known that heart diseases have different influences on the population depending on the sex of the individual. In addition, disease complications, evolution and prognosis may be very different. Therefore, sex has recently been added to the list of factors considered in comparative analyses of influences on heart disease. Heart transplantation is the treatment of choice for the subgroup of patients with evolved cardiopathies, advanced functional status and optimized medical treatment who are without conventional surgical options. Previous clinical and experimental reports have suggested that women who undergo transplantation suffer more complications than men and therefore have a worse prognosis. Female sex has also been linked to increased rates of infection, fatal rejection, renal dysfunction, and vascular graft disease, as well as poorer survival¹⁻⁷.

The objective of this study was to analyse the differences between male and female transplant patients in Spain and the influence of gender on survival.

METHODS

This analysis includes almost all patients transplanted in Spain since the inception of our cardiac transplantation program (May 1984) through December 2005 and comprises 4,408 transplants (762 women and 3,646 men) performed in the centres listed in table 1. We performed a univariate analysis of

patient, donor, surgical, immunosuppressive, complications, and survival characteristics. Survival curves were compared, and factors were identified that were associated with early (first month) and 1-, 5- and 10-year mortality. Values are expressed as mean ± standard deviation and as percentages. Univariate comparisons were performed with the analysis of variance and (2 tests. Values are expressed by the multivariate hazard ratio (HR) and 95% confidence interval (CI). Significance was set at p < 0.05.

RESULTS

The male:female ratio for patients who are transplanted in Spain is approximately 5:1. Women are more likely to be younger, to have a diagnosis of idiopathic dilated cardiomyopathy and to have fewer cardiovascular risk factors. More often they were transplanted in emergency and with younger males and body mass index similar to theirs (tables 2 and 3). There were significant differences in the surgical variables analysed, but these are not relevant from a clinical standpoint. The use of cyclosporine and steroids was lower in women (table 4). Women developed acute graft failure more frequently. At follow-up, women had a higher incidence of bone complications and a lower incidence of dyslipidaemia, hypertension, digestive complications or tumours (table 5).

TABLE 3. Univariate analysis of donor characteristics

Variables	Women	Men
Age (years)*	29 ± 14	31.9 ± 12.5
Men *	59.2	76.2
Body mass index *	23.3 ± 4	24.6 ± 3.5
UCI period	2.9 ± 10	2.7 ± 6
Cause of death*		
Traumatic brain injury	42.4	46.8
Stroke	41.9	37.6
Other	15.7	15.6

Values are expressed as mean ± standard deviation or as percentages.
*p < 0.05.

TABLE 4. Univariate analysis of surgical and immunosuppression characteristics

Variables	Women	Men
Ischemic time (min)*	185 ± 65	179 ± 64
Operative time (min)*	131 ± 63	126 ± 51
Surgical technique*		
Standard	72	76
Bicaval	28	24
Emergency transplant*	26.8	23.4
Induction	74.5	74
Cyclosporine*	71.9	85.2
Azathioprine	57.7	60.6
Steroids*	93.4	95.3

Values are expressed as mean ± standard deviation or as percentages.
* p < 0.05.

TABLE 5. Univariate analysis of complications during follow-up

Variables	Women	Men
Acute graft failure *	17.4	13.5
Number of rejections per patient	1.1 ± 1.5	1 ± 1.4
Graft vascular disease *	6.9	10.7
Infection	0.79	0.82
Hypertension *	36.1	49.3
Insulin dependent diabetes mellitus	19.9	23.2
Need for dialysis	5.1	5
Need for pacemaker	4.2	5.2
Musculoskeletal complications *	15.5	10.9
Neurological complications	16.1	14.8
Digestive complications*	12.1	16
Dyslipidaemia *	38	45.4
Tumours*	9	12.5

Values are expressed as mean ± standard deviation or as percentages.
*p < 0.05.

Survival analysis

Initially, women had lower survival rates through the first year, but by five or ten years post-transplant, survival rates in women were similar to those in men (figs. 1-4). We identified many significant variables in the multivariate analysis; however, when the analysis was performed for each sex, we observed that the number of variables associated with mortality was significantly lower in women (tables 6 and 7).

DISCUSSION

Relating cardiovascular complications and outcomes of cardiac surgery to the patients' sex is a relatively new concept, which may have started from observations in large multicentre trials that certain drugs were active exclusively in one sex. This has led to the study of therapeutic responses in men and

TABLE 6. Factors associated with mortality in men

	HR (95% IC)	p
Early		
Underlying disease (compared to others)	0.5 (0.3-0.7)	0.001
Cause of death of the donor (relative to others)	0.4 (0.2-0.9)	0.01
Outpatient status of the patient	0.5 (0.4-0.7)	0.0001
Acute graft failure	4.8 (3.3-6.7)	0.0001
Peripheral vascular disease	0.1 (0.1-0.9)	0.04
Operative time (min)	1.005 (1.002-1.007)	0.0001
At 10 years post-transplant		
Renal dysfunction	1.3 (1.1-1.6)	0.01
Previous diabetes mellitus	1.3 (1.1-1.7)	0.008
Induction	0.8 (0.7-0.9)	0.03
Cyclosporine	0.6 (0.5-0.8)	0.0001
Azathioprine	1.7 (1.4-2.0)	0.0001
Steroids	0.3 (0.2-0.5)	0.0001
Dialysis	2 (1.5-2.8)	0.0001
Neurological complications	1.5 (1.2-1.8)	0.0001

CI: confidence interval; HR: hazard ratio.

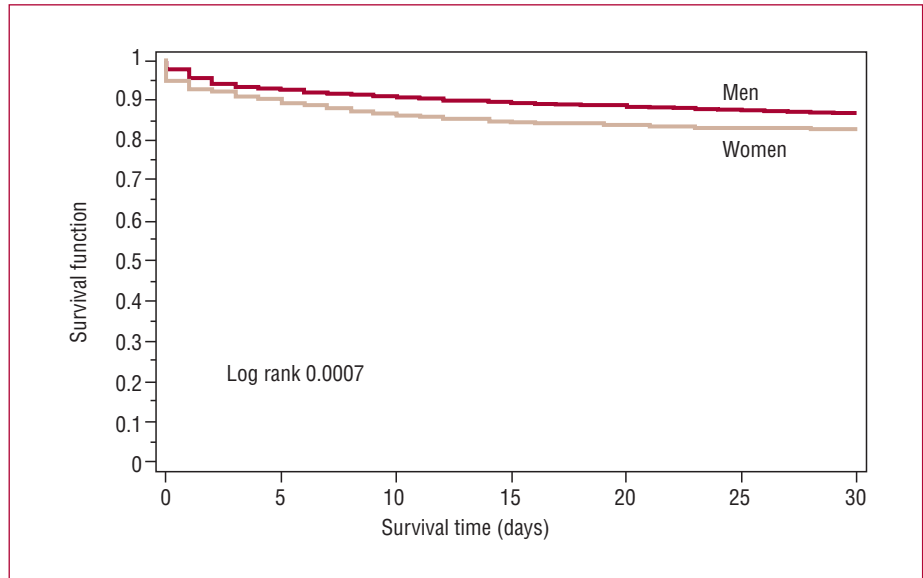


Fig. 1. Actuarial survival curve at day 30.

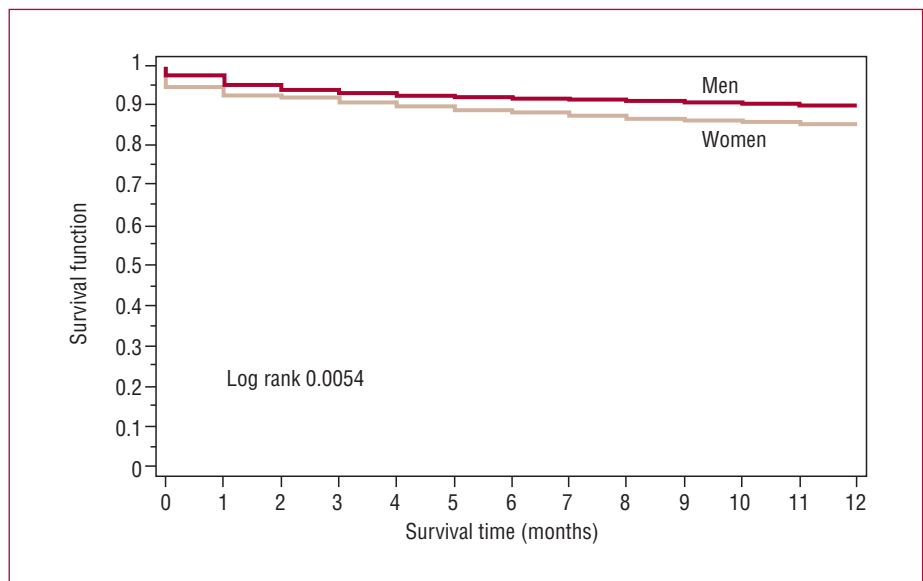


Fig. 2. Actuarial survival curve at the first year.

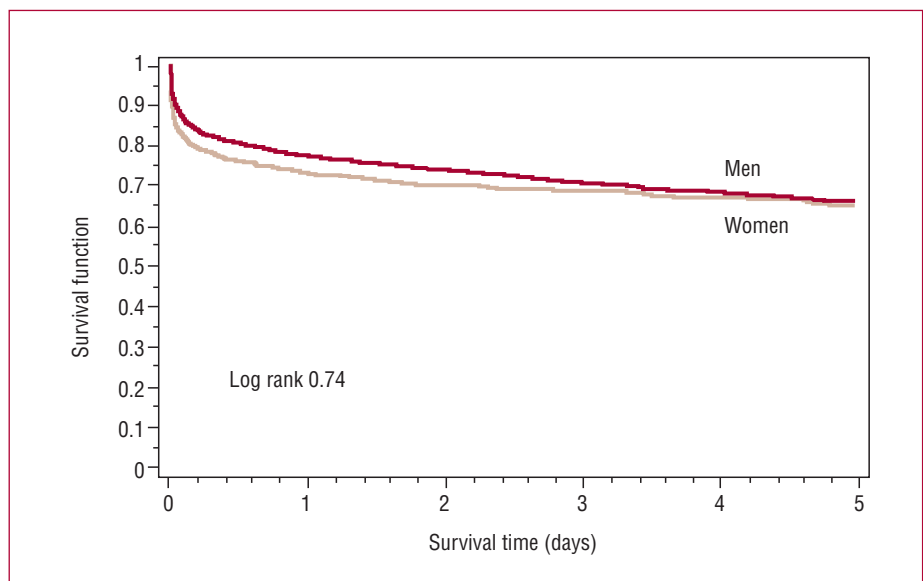


Fig. 3. Actuarial survival curve at the fifth year.

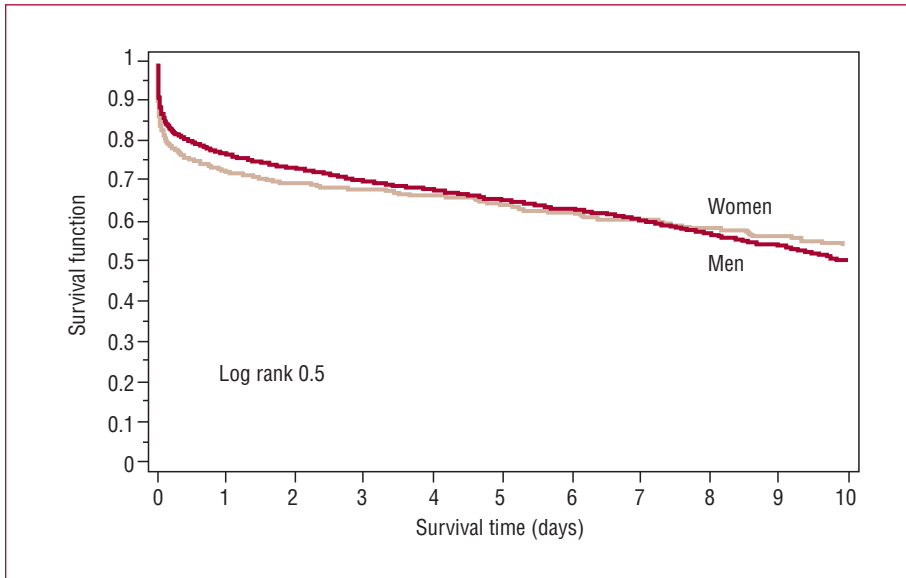


Fig. 4. Actuarial survival curve at the tenth year.

TABLE 7. Factors associated with mortality in women

	HR (95% IC)	p
Early		
Mechanical Ventilation	2.9 (1.6-5.1)	0.0004
Acute graft failure	3.9 (2.2-7.0)	0.0001
At 10 years post-transplant		
Induction	0.6 (0.4-0.9)	0.003
Fungal infections	2 (1.1-3.9)	0.03
Dialysis	2.3 (1.1-4.9)	0.03

women in all aspects of cardiology. In the heart transplantation literature, several small series of nonrandomized studies (likely involving patients with significant differences in baseline characteristics) have reported that hearts from women may develop more graft vascular disease, as well as other complications that negatively impact survival¹⁻⁷. These associations are unclear even in records with a large number of patients. First, in the International Registry of Heart Transplantation for adult patients, female gender was associated with increased mortality⁸. but only in the analysis from 1999, as this association was not previously found in the International Registry of Pediatric Heart Transplant, in which survival was worse at 1 and 5 years in females⁹. Furthermore, other international registries have found no differences between the sexes¹⁰⁻¹².

In the multivariate analysis published biannually along with the results of the Spanish Groups of Heart Transplantation, no significant correlation between sex and mortality was ever present¹³⁻¹⁶. Therefore, the reason for this analysis was to clarify this point by

analysing and taking into account sex to raise awareness about the Spanish experience. From this analysis, it is difficult to draw conclusions. However, we observed that the clinical profile in women was generally better than in men, and that the lower initial survival in women was due to an increased incidence of acute graft failure; although the cause of this acute failure was unknown, we believe that it was due to the greater proportion of women who underwent urgent transplantation. When the survival curves were analysed, we observed that after an initial decrease in postoperative survival rates, the curve for women was fairly stable and even exceeded the survival curve for men, whose average slope of decline was greater, perhaps related to their higher incidence of risk factors that were present at baseline or enhanced by the immunosuppressants.

In multivariate analysis for early and 10-year mortality, there were many differences between men and women. We found 14 significant variables that predicted mortality in men and only five in women. This may be due to sex differences, but may also be because the number of cases was much lower in women, which significantly affects the multivariate analysis. The only significant variables common to both sexes were acute graft failure and the need for dialysis, which were risk factors for mortality, and the use of induction immunosuppressants, which was protective.

CONCLUSIONS

There were important differences between men and women who undergo cardiac transplantation, but with the exception of early-stage mortality, survival was similar in both sexes.

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A Study of Cardiovascular Disease in Women in Spain: Conclusions and Final Recommendations

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This article details the conclusions and final recommendations of the study on cardiovascular disease in women in Spain carried out by the Spanish Society of Cardiology. Important differences were found between men and women in clinical characteristics, risk factors, diagnostic assessment, treatment and prognosis in most of the conditions studied, but particularly in acute coronary syndrome, heart failure and hypertension. In general, differences in diagnostic and therapeutic procedures work to women's disadvantage. The information available on atrial fibrillation and valvular heart disease is incomplete and studies focusing on these conditions are needed. There is also a need for a program of education and information to raise awareness of inequalities between the sexes both in the general public and among healthcare professionals, and for practical measures that will improve care for women with cardiovascular disease.

Key words: *Cardiovascular disease. Prevention. Sex differences*

Proyecto de estudio sobre la situación de la enfermedad cardiovascular de la mujer en España: conclusiones y recomendaciones finales

En este artículo se presentan las conclusiones y las recomendaciones finales del estudio sobre la enfermedad cardiovascular de la mujer en España, realizado por la Sociedad Española de Cardiología. Hay diferencias notables entre mujeres y varones respecto a las características clínicas, el perfil de riesgo, la realización de pruebas diagnósticas, las medidas terapéuticas y el pronóstico en la mayor parte de las enfermedades estudiadas, sobre todo en el síndrome coronario agudo, la insuficiencia cardíaca y la hipertensión arterial. Las diferencias en el manejo diagnóstico y terapéutico son, en general, desfavorables para las mujeres. No existe información adecuada respecto a la fibrilación auricular y las enfermedades valvulares, por lo que es preciso realizar estudios específicos de estas afecciones. Son necesarias campañas de información y educación para concienciar tanto a la sociedad en general como a los profesionales sanitarios sobre estas desigualdades, así como adoptar medidas que contribuyan a mejorar la atención de las enfermedades cardiovasculares en las mujeres.

Palabras clave: *Enfermedades cardiovasculares. Prevención. Diferencias por sexo.*

A wealth of information exists from reliable sources, such as records and studies carried out by the Spanish Society of Cardiology, its Scientific Sections and Affiliated Societies, on the care status, characteristics

and management of cardiovascular disease in Spain over the last 5-10 years. This information comes from population studies and general records on different diseases that were obtained in both hospital and outpatient environments using appropriate methodology. Therefore, the results are thought to be representative of the majority of patients with cardiovascular disease in Spain.

The large number of patients included in these studies and records, and the significant percentage of

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women, allows for reliable analysis of the gender differences in the management and cardiovascular disease characteristics in Spain of the majority of the most important illnesses. The information obtained and presented in the present study is exhaustive in the field of acute coronary syndrome, heart failure, hypertension and heart transplants. There is less information on auricular fibrillation and heart valve diseases.

In general, among the set of all diseases, there were important differences according to gender. The clinical and aetiological characteristics, the cardiovascular risk factor profile, the performance on diagnostic exams, the therapeutic measures and the prognosis were different between men and women for most of the pathologies and variables studied. In general, and above all in the field of acute coronary syndrome, women were treated unfavourably in relation to men in terms of the adoption of recommended diagnostic measures and therapies, which may bring about a worse prognosis. However, even though gender by itself was an independent prognostic factor of some of these differences, it is possible that the distinct management and prognosis influences other variables such as the distinct initial risk profile and the perception of said risk between women and men, which is discussed below.

For acute coronary syndrome (ACS), the study performed represented an extensive investigation on the influence of gender on the characteristics, the evolution, the management and the prognosis of ACS in Spain. It included information from a defined period (1994-2002) of 48,369 patients [13,405 with NSTEMI-ACS (non-ST segment elevation acute coronary syndrome) and 34,334 with STEMI-ACS (ST segment elevation acute coronary syndrome elevation)]; of which 24.3% were women (26.6% of the patients with NSTEMI-ACS and 23.2% with STEMI-ACS). The results of the investigation should be interpreted in light of the limitations referred to in the corresponding chapter, which relates to the current validity and the possible bias derived from the methodology used.

In the NSTEMI-ACS patients, women had a higher average age than men did (by 6 years on average) and a much more unfavourable cardiovascular risk profile, with higher prevalence of hypertension, dyslipidemia and diabetes, even though the rate of tobacco use of was markedly lower. In terms of cardiovascular antecedents, the proportion of women with antecedents of cerebral vascular accidents (CVA) or angina was similar to that of men, but men displayed a higher atherosclerotic load, which was demonstrated by the higher frequency of antecedents of stroke, coronary revascularisation and peripheral vascular disease. The use of antiplatelets and antithrombotics in the hospital treatment of patients with NSTEMI-ACS was high and similar between men and women. In regards

to other treatments, there were differences in the use of beta-blockers (less in women), which is not clearly explained because a more intensive treatment would be expected for patients with these baseline characteristics (higher risk profile). A higher use of angiotensin convertase inhibitors (ACEI) and diuretics in women was observed, which is thought to relate to the higher prevalence of hypertension and incidence of heart failure during admission. The mortality and the incidence of adverse events (AMI, heart failure and cardiogenic shock) were 50% higher in women, both during the acute phase and at 28 days and at 1 year. However, the multivariable analysis showed that gender is a predicting factor that is independent from hospital mortality even after 28 days. The mortality excess can be explained by other factors frequently related to the female gender, such as diabetes, previous myocardial infarction and age.

In STEMI-ACS patients, women presented a different profile than men, which was similar to the group of patients with NSTEMI-ACS, although there were some differences. The difference in the average age was higher in the patients with ST elevation than with NSTEMI-ACS (8.8 years higher in women), but the prevalence of dyslipidemia was similar. The rest of the differences between men and women were similar to the NSTEMI-ACS group (less prevalence of tobacco users, more hypertension and diabetes and a more frequent history of angina and heart failure, coronary revascularisation and intermittent claudication in women than in men). The percentage of women with STEMI-ACS reperfused with fibrinolysis was lower than the percentage of men. Additionally, the time until reperfusion was longer in women than in men. This delay was produced by a longer arrival time to the hospital (time between the beginning of the pain and admission) and by the delay between the admission and the beginning of reperfusion. In women with STEMI-ACS, similar to what occurred with the ones that suffered from NSTEMI-ACS, differences were detected in the use of pharmacological interventions and of therapeutic resources; considering the higher risk in women; this leads to the suspicion of underuse of these resources for women compared to men. Mortality and hospital complications in women with STEMI-ACS were double those of men. As with NSTEMI-ACS, the mortality at 28 days in patients with STEMI-ACS was very high (11.5%), and the mortality of women per month was double that of men (20%). In contrast to the group of patients with STEMI-ACS, being a woman was found to be an independent predictor factor of hospital mortality at 28 days and at 1 year (increased by 30%).

For heart failure (with studies that included more than 6,000 patients), the prevalence was very high, around 7%, and similar between women and men. For both patients hospitalised for acute heart failure and

for stabilised patients that were controlled during outpatient appointments, women with heart failure were older, had a more unfavourable cardiovascular risk profile (higher prevalence of hypertension and diabetes), fewer antecedents of ischemic cardiovascular disease and a distinct aetiology (greater frequency of ischemia in men and of hypertension and other non-ischemic causes in women). Likewise, and likely in relation to this aetiology, the physiopathological type of heart failure was also distinct: there was a higher proportion of cases with conservation of systolic function in women and with depressed systolic function in men. No big differences were observed in the diagnosis techniques used except for a higher use of exams to detect myocardial ischemia (ergometry, coronarography) in men. The determination of the ejection fraction by echocardiography was similar in both genders. No great differences were observed in terms of pharmacological treatment either, although the use of ACEI and beta-blockers was slightly, yet significantly, lower among women. Mortality, both in the hospital and long-term, was similar between women and men, although the incidence of readmission for heart failure decompression was higher in women, which could influence the differences observed in their treatment.

For hypertension, the analysed records included almost 50,000 patients and concluded that women with hypertension present important differential characteristics compared to men: increased age; higher prevalence of obesity, diabetes, hyperlipidemia and metabolic syndrome; lower tobacco use; and distinct involvement of target organs (more renal and cerebral vascular alterations, atrial fibrillation and heart failure, and less problems related to ischemic cardiovascular disease and peripheral arterial disease). No significant differences were observed in the usage of pharmacological treatments, although there was a tendency of higher use of some medications, such as diuretics or nitrates and above all non-cardiovascular medication (like non-steroid anti-inflammatory medication). Arterial pressure control was not adequate in most of the studied population, and no significant differences were observed between women and men.

There is little information on the prevalence of atrial fibrillation and the knowledge of its management characteristics, treatment and prognostic and long-term complications that can be derived from local and foreign studies. Therefore, it seems necessary to design and perform broad, multicentre studies that include the entire national territory. The objectives should be to study its prevalence, both generally and by subgroups of age and gender (epidemiologic population studies), and to better understand its clinical characteristics, the associated diseases, the treatment and the long-term prognosis (transversal and longitudinal multicentre records).

With respect to heart valve diseases, there are no integral national records that allow definite conclusions. Data from the autonomous community of Andalusia indicate that mortality, both from non-rheumatic aortic valve disease and from rheumatic mitral valve disease, is higher in women than in men of any age. In the Andalusian records of valve diseases, some differential data in relation to gender was observed: an increase in the number of hospital admittances among women for severe valve disease and some associated comorbidities such as anaemia; a higher prevalence of rheumatic valve disease in women than in men; and a lower incidence of left ventricular dysfunction in men. In contrast, there were no differences in the use of valve surgeries between genders. As with auricular fibrillation, the lack of national information makes it necessary to design and carry out wider studies.

Finally, in relation to cardiac transplantation, exhaustive data analysis of the National Record of Cardiac Transplantation allows for the extraction of reliable conclusions on gender differences in this field (762 women compared with 3,646 men with transplants in Spain from May 1984 to December 2005). The male to female transplant ratio was 5:1. Women were younger (45 ± 18 versus 51 ± 14 years; $p < 0.05$) and had a higher incidence of idiopathic dilated cardiomyopathy (39.8% versus 31.3%; $p < 0.05$) and fewer cardiovascular risk factors (hypertension, 16.2% versus 23.1%; $p < 0.05$; dyslipidemia, 25% versus 36%; $p < 0.05$). Women more frequently had heart transplants in urgent situations (26.8% versus 23.4%; $p < 0.05$) and suffered from acute graft failure (17.4% versus 13.5%; $p < 0.05$). During follow up, they presented with a higher incidence of bone complications (15.5% versus 10.9%; $p < 0.05$) and lower incidence of dyslipidemia (38% versus 45%; $p < 0.05$), hypertension (36% versus 49%; $p < 0.05$), digestive complications (12% versus 16%; $p < 0.05$) and tumours (9% versus 12.5%; $p < 0.05$). The short-term survival probability was lower ($p < 0.05$), but similar to men in the medium and long-terms ($p = 0.6$). The multivariable analysis showed 14 variables that were associated with mortality in men and only 5 in women. It can be concluded that there are important differences between the number of men and women who received transplants in Spain, which can be partially explained by the lower incidence of ischemic cardiovascular disease at the age in which heart transplants are performed; however, other factors probably exist to explain such large differences. The survival probability, except in the early phase, was similar for both genders.

This report detected differences between men and women in the clinical and demographic profile and in the use of therapeutic resources that explain some of the discrepancy in mortality and morbidity observed in women, which was more evident in more serious

occurrences such as heart failure and, above all, in acute coronary syndrome. The higher prevalence of diabetes, hypertension, obesity and concomitant diseases and the total risk profile in woman can influence these differences in an important way because the gender role by itself is diluted and reduced when multivariable analyses are performed. There are opportunities for improvement that should be highlighted by women-oriented campaigns that raise awareness of ischemic cardiovascular disease, which affect women as dramatically as other diseases already included in the preventive mentality of women such as breast cancer. On the other hand, programs are needed that change the attitude of all health care areas to improve the early identification of women with ACS and to achieve an optimisation of treatment in real practice in accordance with the recommendations of the guidelines from different scientific societies. These programs and campaigns should also place emphasis on the remaining diseases related to ischemic cardiovascular disease, such as heart failure and arterial hypertension, among others.

Some specific recommendations are presented below:

- Campaigns to disseminate the results of the present report both among the general population (general means of communication: printouts, audiovisuals and electronics, press roundtables, press notes from the Ministry and the Spanish Society of Cardiology, both individually and collectively) and in the scientific community (cardiologists and health professionals in general through news, interviews, and the like in the health-related media, presentations at scientific congresses, publications in scientific magazines, books, pamphlets and others).

- Specific dissemination campaigns at meetings, congresses and generally in areas specifically related to women. The role of the Observatory of Women's Health of the Ministry of Health and Consumption should be predominant in these campaigns.

- Use of the information obtained in the present report within the strategies of the Ministry of Health

and Consumption: internal diffusion, publishing of monographs, and so on. The discussion of these data would be very interesting in forums where representatives from autonomous sanitary administrations (inter-territorial councils or ad hoc committees) come together with an aim to promote coordinated actions among all the autonomous communities.

- Publishing of a monograph number of Spanish Cardiology Magazine as a supplement containing the present report findings.

- The design and performance of scientific studies over the next years in fields where the existing information is scarce and does not cover the entire national territory (essentially in the area of atrial fibrillation and valve diseases). In this regard, collaboration between the Ministry of Health and Consumption and the Spanish Society of Cardiology would be of great interest.

- The design and performance of scientific studies over the next years in the field of ischemic cardiovascular disease, heart failure and hypertension to evaluate the changes produced in the characteristics, management and prognosis of cardiovascular diseases throughout the years. The data obtained with these studies would indicate the effectiveness of the actions performed to improve the care of women with cardiovascular disease in Spain.

- Undertaking a new report on the gender differences in cardiovascular disease in Spain within 5 years, which would aim to solidify the changes and improvements that have been achieved.

- Finally, the adoption of measures that allow for or facilitate a higher presence of women in clinical studies that evaluate diagnoses or therapeutic measures of different cardiovascular diseases would be of great interest because the participation of women is low in the majority of the available studies upon which most of the current recommendations are based. Health administrations and scientific societies should promote the undertaking of trials and studies specifically designed for women.