

Cardiovascular Disease in Women (II)

Ischemic Heart Disease in Women: Clinical Presentation, Non-Invasive Testing, and Management of Acute Coronary Syndromes

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Cardiovascular disease is the leading cause of death in women. Because of the protective effects of estrogens, ischemic heart disease occurs predominantly in the postmenopausal period and, therefore, much later than in men. The proportion of women with acute coronary syndromes who present with typical chest pain is the same as in men. Nevertheless, atypical chest pain, which is usually associated with a lower likelihood of significant coronary disease, occurs more frequently in women. It is within this context that the sensitivity and specificity of the non-invasive tests used for diagnosing ischemic heart disease are reviewed. In addition, the clinical characteristics, treatment and prognosis of acute coronary syndromes in women are described, while highlighting the contributions made by age and disease severity at presentation to the higher short-term mortality observed in female patients after acute myocardial infarction.

Key words: Angina. Myocardial infarction. Women.

Cardiopatía isquémica en la mujer: presentación clínica, pruebas diagnósticas y tratamiento de los síndromes coronarios agudos

Las enfermedades cardiovasculares son la principal causa de muerte en la mujer. La cardiopatía isquémica, debido al efecto protector de los estrógenos, suele aparecer en la posmenopausia y, por lo tanto, bastante más tarde que en los varones.

Las mujeres con síndrome coronario agudo presentan dolor típico en la misma proporción que los varones; sin embargo, la presencia de dolor atípico, que suele acompañarse de una menor incidencia de lesiones coronarias, es más frecuente en la mujer; en este contexto se discute la sensibilidad y la especificidad de las pruebas no invasivas para el diagnóstico de la cardiopatía isquémica.

Se describen las características clínicas, el tratamiento y el pronóstico de los síndromes coronarios agudos en las mujeres, y se resalta la importancia de la edad y la gravedad de la presentación clínica en la elevada mortalidad del infarto agudo de miocardio en mujeres.

Palabras clave: Angina. Infarto de miocardio. Mujeres.

EPIDEMIOLOGY

Ischemic heart disease in women normally occurs in the postmenopausal period and, thus, at least a decade later than in men. Even though cardiovascular disease is the most important cause of mortality in women, a

large percentage of women are unaware of this. In a survey conducted in the United States, the great majority of women between 25 and 44 years old believed that breast cancer was the leading cause of death among them.¹ In general, society considers that this disease is a health problem that basically affects men.

Specifically, in 1998, cardiovascular diseases caused 37% of all deaths in Spain, 34% of which were deaths in men and 43% in women.² Disorder of the vascular territory also differs depending on sex. Of all cardiovascular deaths in men, 37% were due to ischemic heart disease, 26% to cerebrovascular disease, 25% because of other cardiovascular disease, and 12% were due to heart failure. In contrast, 31% of deaths in women were caused by cerebrovascular disease, followed by 24% due to ischemic heart

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TABLE 1. Estimation of the Number of Infarctions and Deaths at 28 Days, According to Age and Sex

	AMI, n			95% CI	Dead at 28 Days, n		
	25-74 Years	≥75 Years	Total		25-74 Years	≥75 Years	Total
Men	28 415	17 270	45 685	44 060-47 309	10 719	12 786	23 505
Women	6811	15 999	22 809	21 663-23 955	3075	12 120	15 195

Taken from Marrugat et al.³

disease, 26% due to other cardiovascular diseases, and 19% due to heart failure. Acute myocardial infarction accounts for 61% of the deaths from ischemic heart disease in women. Table 1 shows the estimation of the total number of cases of fatal AMI in men and women for 2002 in Spain, according to the age of the patients. It can be seen that men present a greater number of heart attacks in the 25-74 year old age-group, whereas 70% of the cases in women occur in the 75-year-old age-group; total 28-day mortality in the latter age-group is 76%, without apparent differences between the 2 sexes.³

Recent data from the World Health Organization demonstrate that cardiovascular mortality in general, secondary to ischemic heart disease, has decreased almost linearly by approximately 2% per year in Western European countries from 1970 to 2000 in patients aged from 45 to 74 years old (Figure 1). There was an increase in mortality from ischemic heart disease in both men and in women in Spain between 1970 and 1975; however, there has been a highly significant global reduction of 33% in men and 47% in women in the last 25 years, corresponding to annual age-adjusted changes of -0.75% for men and -1.22%

for women ($P<.0001$ for both sexes).⁴ This improved prognosis is related to changes in diet, lifestyle, and new cardiovascular treatments.

CLINICAL PRESENTATION

Despite the importance of the health problem presented by ischemic heart disease in women, the specific characteristics of clinical presentation, treatment, and prognosis have been barely studied, mainly due to the low numbers of women included in clinical trials. It is common for them to be excluded either because they are of childbearing age or are elderly (the period in which prevalence increases in women), and due to the concomitant diseases associated with old age.

Ischemic heart disease occurs predominantly as chest angina in women, whereas in men it does so in the form of acute myocardial infarction and sudden death. The Framingham study found that ischemic heart disease initially presented as chest angina in 65% of women and in 35% of men, whereas infarction or sudden death were the first manifestation in 37% of women and 63% of men.⁵ These data are similar to those obtained recently in the SAMII registry in the

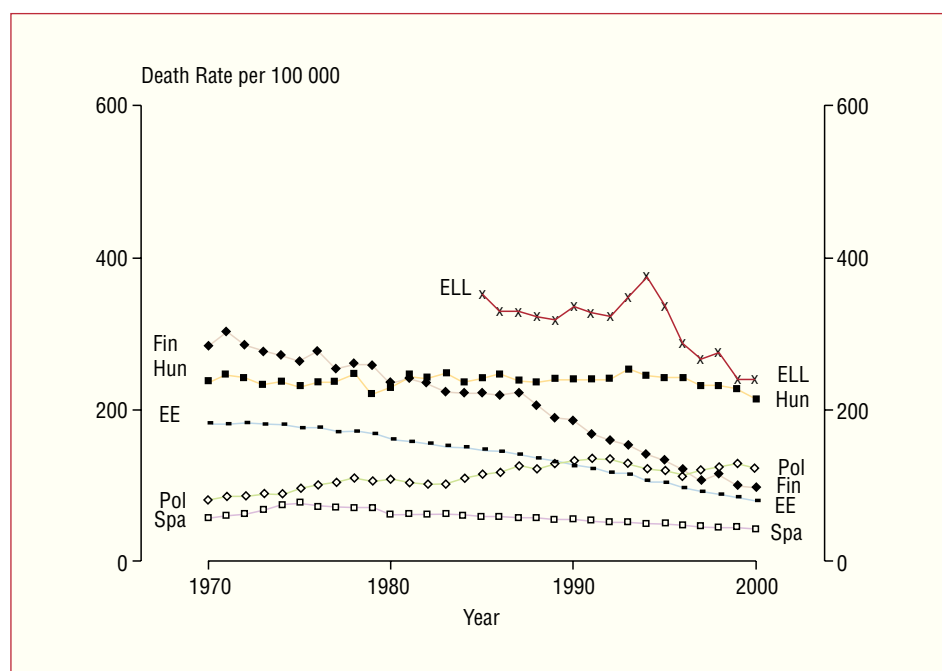


Figure 1. Mortality trends due to ischemic heart disease in 1970-2000 for women between 45 and 74 years old. Austria, Belgium, Denmark, England and Wales, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Scotland, Spain, Switzerland, Sweden. EE indicates East Europe; Fin, Finland; Hun, Hungary; Pol, Poland; Spa, Spain; ELL, Estonia, Latvia, Lithuania. Taken from Kesteloot et al.⁴

United Kingdom which consecutively included 6 women and 6 men with this disease admitted to each hospital. In a sample of over 1000 patients <70 years old, 42% presented acute myocardial infarction, with a significantly greater proportion of men than women (45 vs 38%; $P=.02$).⁶ In addition, the GUSTO IIB study, in which 30% of the participants were women, revealed that presentation with ST-segment elevation was significantly lower in women compared to men (27.2 vs 37%; $P<.001$).⁷

Nevertheless, the clinical symptomatology of AMI or unstable angina is similar to that of men, since a high proportion of women (70%) present chest pain just the same as men; the percentage of men and women diagnosed with acute coronary syndrome without thoracic pain is also similar. However, after adjusting for age and diabetes, women more frequently present nausea, vomiting and indigestion, and also complain more often of pain in the middle of the back and jaw. Premenopausal women tend to more frequently present atypical symptoms than postmenopausal women, whereas elderly women can present sudden dyspnea and less pain in the arms and less profuse sweating; the latter features are also present in older men.⁸⁻¹¹

Data from the CASS study, which was done almost 30 years ago, demonstrated that angina with characteristics typical of coronary ischemic pain in women (retrosternal, during exercise and when relieved by rest or nitroglycerin) was associated with significant coronary lesions in more than 80%; however, when the angina was atypical, coronary lesions were demonstrated in only 40% of women, compared to more than 70% of men with atypical symptoms.¹²

Atypical Angina

Recently, the NHLBI sponsored the WISE study in women (Women's Ischemia Syndrome Evaluation), carried out in four American centers with the following triple aim: *a*) to optimize the assessment of symptoms and diagnostic tests for coronary ischemic disease; *b*) to explore the mechanisms of symptoms and myocardial ischemia in the absence of epicardial coronary artery stenosis; and *c*) to assess the influence of reproductive hormones on symptoms and response to diagnostic tests.¹³ The data obtained in this study showed that, in contrast to the CASS study data, 65% of women with coronary atherosclerotic lesions do not present typical angina. Furthermore, many of the symptoms of women without significant coronary lesions can be due to microvascular ischemia or can appear in the context of coronary vasoconstriction.¹⁴ Two studies conducted in our center demonstrated that women with angina, myocardial ischemia and angiographically normal coronary arteries had vasoconstrictive responses to intracoronary acetylcholine that improved after

administration of percutaneous estradiol; we verified in another group of women that coronary vasoconstriction was also associated with abnormal responses in the humeral artery that were reversible with estradiol.^{15,16} The WISE study researchers have described limited responses in coronary microvascular flow to the administration of intracoronary vasodilators; however, the relevance of these findings regarding chest pain symptoms in daily life remains to be determined.¹⁷ Neither is the correlation between abnormalities in epicardial flow studied in the catheterization laboratory and myocardial ischemia analyzed via conventional stress tests clear.¹⁸ As new, and much more sophisticated, imaging techniques have become available—such as magnetic resonance imaging and single photon emission computed tomography—it has been found that women with chest pain without coronary lesions had important changes in high-energy phosphates during an isometric stress test (hand-grip) compared to women in the control group.¹⁹ In another study that included women and men with chest pain and angiographically normal coronary arteries, magnetic resonance imaging detected a smaller increase in subendocardial perfusion in relation to the epicardium after stimulation with adenosine than in normal subjects.²⁰ It still remains to be determined what the impact could be on syndrome X (chest pain and angiographically normal coronary arteries) of changes in cortical activation by visceral afferent signals that cause abnormal perception of pain during effort, with or without ischemia.²¹

In summary, vasospastic angina, microvascular angina, and coronary flow reserve abnormalities are more prevalent in women, usually presenting in the form of atypical chest pain, and have a better prognosis than coronary atherosclerosis.²²

DIAGNOSTIC TESTS IN THE ASSESSMENT OF ISCHEMIC HEART DISEASE

Women as well as men with symptoms of ischemic heart disease symptoms, as well as men, should be studied to confirm the diagnosis and extent of the disease. Risk stratification is based on combining a set of parameters from the medical record, particularly the presence of classic risk factors, as well as analysis of symptoms and tests for ischemia and other laboratory data that are discussed below.

Non-Invasive Diagnostic Tests

The exercise stress test continues to be the basic test in the non-invasive diagnostic study of myocardial ischemia, appropriately interpreted. However the pretest probability of ischemic heart disease should be ascertained in women, especially in younger or middle aged ones, in whom a false positive result can occur, in order to have an adequate interpretation. A preliminary estimation of

risk for each woman should initially be done, particularly of having ischemic heart disease according to medical record data (risk factors), with special emphasis on the characteristics of the coronary pain, as shown in Table 2.²³ Risk can be calculated with any of the currently available risk scores. Non-invasive diagnostic studies with an exercise stress test, plus imaging when necessary, is recommended in symptomatic women who have an intermediate to high pretest probability of presenting ischemic heart disease. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that the exercise stress test is indicated in women with an intermediate pretest probability (symptoms and risk factors), normal baseline electrocardiogram (ECG) and who are capable of maximal physical exercise. However, the metaanalysis by Kwok et al,²⁴ which included 3721 women, demonstrated that the exercise stress test in women had lower sensitivity (61% vs 72%) and specificity (70% vs 77%) compared to the median obtained in a group of almost 2000 men. Other parameters of the exercise stress test that determine long- and short-term prognosis in women are maximal exercise capacity and heart rate recovery.^{25,26} These parameters, together with others such as the DUKE treadmill score, have not yet been incorporated into the ACC/AHA guidelines, but definitely would increase the diagnostic precision of changes in the ST segment during exercise stress testing in women.

Stress Echocardiography

Echocardiography provides very valuable information on systolic and diastolic ventricular function, how the heart valves are valve function and myocardial ischemia. Stress can be applied with treadmill or stationary bicycle; dobutamine is normally used in pharmacologic stress echocardiography, since it seems to provide better sensitivity than dipyridamole or adenosine, especially in single-vessel disease. There is data on more than 1000 women studied with suspected coronary disease demonstrating that stress echocardiography has a sensitivity of 81%, reaching 89% in cases of multi-vessel disease, and a specificity of 86%; there seems to be no differences regarding sensitivity and specificity

between men and women with this imaging technique. This test has good cost-effectiveness, especially in women at intermediate risk of ischemic heart disease, since it leads to better selection than the simple exercise stress test in women with severe ischemia where a coronary angiography should be done.²⁷

A recent study has verified that women presenting positive dobutamine stress echocardiography have a ten-fold higher risk of death at 5 years than women with negative test.²⁸

Nuclear Stress Test

Myocardial perfusion can be studied via single photon emission computed tomography (SPECT), a nuclear technique, which makes it possible to visualize global and regional perfusion defects, and ventricular function and volume. Nevertheless, this technique has some limitations in women due to the presence of breasts, which can yield a false positive result, and to having smaller hearts, which is frequently the case in women.²⁹ However, these problems encountered with 201Tl SPECT can be eliminated by using 99mTc-sestamibi SPECT, which improves image quality. This isotope was used in a study of 163 patients and yielded a sensitivity and specificity of 87% and 91% in women and 88% and 91% in men, respectively.³⁰ A sensitivity and specificity of 85% have been reported in pharmacologic stress tests with 99mTc-sestamibi.³¹ Data from more than 5000 women studied showed a significant increase in risk of cardiac events in the presence of abnormal perfusion findings; 3-year survival is 99% in women without perfusion defects and falls to 85% in studies on ischemia affecting the territories of the three major coronary vessels.³²

Regardless of the test used to screen for ischemia, women, as well as men, should be referred to coronary angiography when indicated.

Various examples have been published on the underuse of coronary angiography in women where this is clearly indicated. The women included in the SAVE study who had chest angina before the myocardial infarction were significantly less often referred to coronary angiographies than men (15.4% vs 27.3%; $P > .001$) and, in addition, a smaller proportion underwent revascularization (5.9% vs 12.7%) before the AMI.³³ The results of a survey also demonstrated that women, especially colored women, had a smaller probability of being referred to coronary angiography than men.³⁴

Other Imaging Modalities

Coronary angiography with computerized tomography (CT) detects and quantifies the quantity of calcium (an atherosclerotic disease marker) in the coronary arteries. In a study including 539 women referred to

TABLE 2. Pretest Probability of Ischemic Heart Disease in Women According to Age and Symptoms

Age, y	Typical/Definite Angina	Atypical/Probable Angina	Chest Pain Without Angina	Asymptomatic
30-39	Intermediate	Very low	Very low	Very low
40-49	Intermediate	Low	Very low	Very low
50-59	Intermediate	Intermediate	Low	Very low
60-69	Discharge	Intermediate	Intermediate	Low
>70	Discharge	Intermediate	Intermediate	Low

Taken from Mieres et al.²³

catheterization, none of the 220 with angiographically normal coronary arteries presented coronary calcification, with a negative predictive value of 100%, whereas those with calcium scores between 100 and 400 had a higher prevalence of obstructive lesions.³⁵ Another study demonstrated that women with higher calcium scores had greater 5-year mortality.³⁶

There are still few data on the value of adding calcium scores to classic risk factors for risk stratification in asymptomatic women. Until such studies become available, the assessment of coronary calcium via CT should be reserved for women at intermediate risk of ischemic heart disease.²³

Magnetic resonance imaging is very flexible and makes it possible to visualize the coronary arteries and flow, as well as assess myocardial perfusion and regional and global ventricular contractility and identify myocardial necrosis. Although there is still little clinical experience, initial data makes it possible to state that dobutamine stress magnetic resonance imaging is possibly better than dobutamine stress echocardiography for the quantitative assessment of coronary lesions. This technique, as well as echocardiography, does not depend on ionizing radiation, which would need to be taken into account if it was available in all hospitals, although making recommendations regarding its use for risk stratification would currently be premature.²³

Another non-invasive technique that has an important role in cardiovascular prognosis is the carotid artery intima-media score, measured through B-mode sonography. However, this technique still presents problems regarding standardized measurements and the absence of population data,²³ which means that, currently, it does not seem to add anything to risk stratification in asymptomatic women.

Figure 2 presents the algorithm for assessing women with symptoms via the exercise stress test and other imaging techniques.

Electrocardiographic, Blood Test, and Physical Exercise Data in Risk Stratification

The WISE study has provided important information on the independent predictive value of the ECG at rest to identify women with coronary lesions. Of the 850 women with a baseline ECG who underwent coronary angiography to investigate thoracic pain, it was reported that 39% had significant lesions in one or more vessels; furthermore, 13% had Q-waves in two or more consecutive leads, including 7% without a previous history of infarction. When the analysis was adjusted, it was shown that Q-waves in the inferior wall and T-wave inversion independently predicted the presence of coronary lesions. When the results of the perfusion tests with isotopes were taken into account, negative T-waves in the baseline ECG added

independent predictive value. These parameters should be incorporated into future algorithms for diagnosing ischemic heart disease in women.³⁷ Other rarely measured electrocardiographic parameters, such as the QRS-T angle and QT interval adjusted for age and sex, were predictive of cardiovascular events in women participating in the WISE study.³⁸

This study has demonstrated that, in women who underwent cardiac catheterization due to suspected ischemia, better physical condition was independently associated with fewer coronary risk factors, less coronary artery disease and fewer cardiovascular events; however, obesity measurements (Body Mass Index, waist circumference, waist-hip ratio, or waist-height ratio) did not have any independent association with events during follow-up.³⁹

The WISE study has also identified mild kidney failure (serum creatinine, 1.2-1.9 mg/dL) as an independent predictor of significant coronary disease,⁴⁰ and anemia, defined as hemoglobin <12 g/dL, as a factor predictive of adverse cardiovascular events during a follow-up of 3.3 years.⁴¹ This study confirmed that inflammatory markers predict cardiovascular risk in women, and that the inflammation can act by not only promoting atherogenesis, but also by destabilizing vulnerable plaque.⁴²

TREATMENT OF ACUTE CORONARY SYNDROME

Clinical Characteristics

There are important differences between women and men regarding the clinical manifestations of acute coronary syndromes. In the GUSTO IIB study, women were significantly older than men, had higher rates of diabetes, hypertension with higher cholesterol, prior angina, heart failure, and cerebrovascular disease. However, fewer were smokers, and they had less peripheral vascular disease and prior myocardial infarction. At the time of the acute event they had higher heart rate, higher blood pressure, and a worse Killip class.⁷ The DESCARTES registry, carried out in 2002 by the Ischemic Heart Disease Section of the Spanish Society of Cardiology, included 1877 patients with acute coronary syndrome with non-ST-segment elevation, 630 of whom were women (34%).⁴³ The women were significantly older than the men (69.8 vs 65.5 years), and had more hypertension, diabetes and insulin-dependent diabetes, as well as more cases of a background of heart failure, although they presented less incidence of peripheral vascular disease, myocardial infarction and prior coronary revascularization. As in the GUSTO IIB study, women had more hypertension and tachycardia (unpublished data) at the time of admission. The multicenter PRIAMHO II registry was carried out in 2000 with a total of 6105 patients with acute

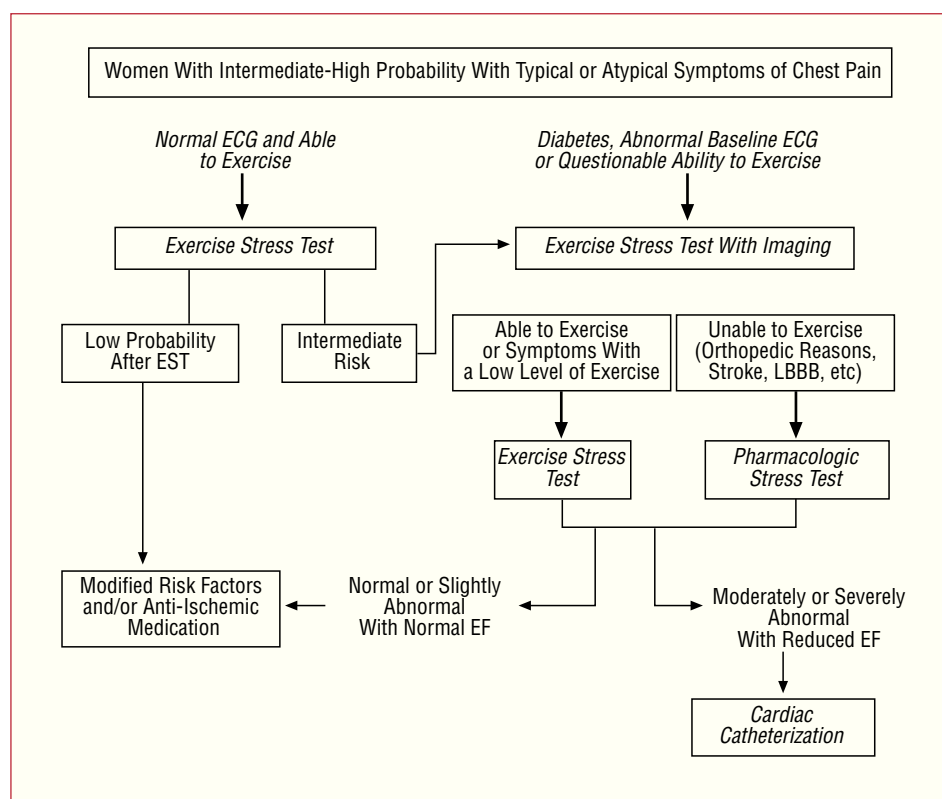


Figure 2. Algorithm for assessing symptomatic women via exercise stress testing or cardiac imaging. LBBB indicates left bundle branch block; ECG, electrocardiogram; EF, ejection fraction; EST, exercise stress test. Taken from Mieres JH, et al.²³

myocardial infarction, 1568 of whom were women (25.3%). Although it presents practically identical data, it recorded a greater frequency of acute myocardial infarction with non-ST-segment elevation or left bundle branch block, and worse Killip class at admission.⁴⁴ Thus, the clinical data recently obtained in Spain are similar to those reported in multinational studies more than a decade ago, and so we can conclude that this pattern is well-defined and has not varied substantially over time. However, as there is a similar or higher proportion of women smokers than men, within a few years there will probably be more clinical presentation of acute coronary syndromes in women who have smoked for more than 20 years, and which can be accompanied by accelerated arteriosclerosis in other vascular territories.

Another very important parameter is delay in going to hospital. In general, women tend to go to hospital later and more often go to the family doctor before going to hospital^{6,45}; this behavior usually has serious consequences in women with ST-segment elevation, since reperfusion therapy is delayed and the odds of saving the myocardium at risk are reduced.

Reperfusion

Unadjusted data show that women with ST-segment elevation acute coronary syndrome in Spain receive different treatment to that given to men. Specifically, the

PRIAMHO II registry found less use of reperfusion in women (43% vs 51%; $P < .0001$), although when adjusted for clinical characteristics, the severity of the clinical picture, and location of the infarction, the importance of sex was not statistically significant.⁴⁴ Very similar results have been published by a group in Israel where, after adjusting for covariates, the difference in the administration of fibrinolytic agents in women disappeared.⁴⁶ However, the British registry carried out during the same period as the PRIAMHO II study did not show absolute differences in the administration of fibrinolytic treatment between men and women (77% vs 82%).⁶

According to clinical practice guidelines, primary angioplasty should be considered the preferred choice regarding reperfusion due to strong evidence of its benefit in women. This treatment avoids cerebral hemorrhage involved in fibrinolytic treatment, which is more common in women. The reduction in relative risk, which is similar between the sexes, leads to a greater absolute benefit due to more serious presentation of an acute myocardial infarction in women.^{47,48}

Antithrombotic Therapy

Antithrombotic agents play a key role in the treatment of ischemic heart disease, both in the acute phase and in secondary prevention. Examination of prescriptions for aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor

antagonists shows that women usually receive less frequently these agents. Specifically, aspirin was administered less frequently to women in the Israeli registry, although this difference disappeared when adjusted for age.⁴⁶ Similarly, in the PRIAMHO II registry, there was a smaller percentage of women than men treated with aspirin (70.5% vs 76.4%; $P<.001$), clopidogrel (11.9% vs 14.4%; $P=.016$) and glycoprotein IIb/IIIa antagonists (10.6% vs 13.1%; $P=.011$), even though there was a greater proportion of women with non-ST-segment acute coronary syndrome.⁴⁴ The underuse of glycoprotein IIb/IIIa antagonists has also been reported in the CRUSADE registry, which included 35 875 women from various American hospitals (41% of the population)⁴⁹; furthermore, they also received less aspirin at discharge. The DESCARTES registry also verified that women received less aspirin than men (85.2% vs 88.8%; $P=.025$), but there were no differences in the administration of thienopyridines or glycoprotein IIb/IIIa antagonists; as in the CRUSADE registry, the percentage of women discharged with aspirin and clopidogrel was significantly lower than men (unpublished data).

Such results from daily practice contrast with the evidence that these drugs are effective in both sexes and that their use is recommended in clinical practice guidelines, especially in women who receive percutaneous coronary revascularization. Specifically, the benefit of clopidogrel added to aspirin for 1 year, after a coronary angioplasty in women, produces a reduction in risk similar to that found in men.⁵⁰ In addition, in the context of percutaneous coronary revascularization, abciximab is as equally effective in men as in women.⁵¹ However, the administration of eptifibatide and tirofiban should be reserved for women undergoing percutaneous coronary intervention during the course of a non-ST-segment elevation acute coronary syndrome or for those included in high-risk groups, especially those with high troponin levels or who are diabetic. These drugs should not be administered in the absence of these indications, since they can even have adverse consequences in women.^{52,53}

Unfractionated heparin and low-molecular-weight heparins are equally effective in both sexes. It should be recalled that unfractionated heparin should be weight-adjusted (especially in small women) and the dosage should follow the guidelines when combined with fibrinolytic treatment. Low-molecular-weight heparins have clear advantages over unfractionated heparin, but when they are administered to elderly people, as in the case of many women with acute coronary syndromes, renal function and low body weight should be taken into account to avoid an overdose. Currently available evidence on the use of bivalirudin in percutaneous revascularization indicates a greater reduction in bleeding, and less in women, compared to unfractionated heparin.⁵⁴

Other Treatments

Less use of beta-blockers in women has also been reported in the context of acute coronary syndromes in the Spanish PRIAMHO II⁴⁴ (44.1% vs 52.4%; $P<.001$) and DESCARTES (64.8% vs 58.6%; $P=.006$) registries, and in the CURE⁵⁵ (79.6% vs 77%; $P<.01$) study; they are also administered less frequently as secondary prevention agents.

Although statins have proven to be equally effective in men as in women, both in the acute phase and in secondary prevention, their use in clinical practice is substandard, as the results of the CRUSADE,⁴⁹ PRIAMHO II,⁴⁴ and DESCARTES registries show that, although the proportion of dislipidemic patients was similar in both sexes, once again they were administered to women less frequently. Another problem involved in statin therapy, which appears in several studies with women, is not only to actually administer the drug in the acute phase, but to achieve an LDL-cholesterol target value of <100 mg/dL, which is only obtained in a small proportion of women.⁵⁶

Angiotensin-converting enzyme inhibitors (ACE inhibitors) were used in a greater proportion of women in the PRIAMHO II⁴⁴ and DESCARTES registries, probably because there were more women with hypertension or diabetes.

Diagnostic Tests During Acute Coronary Syndrome

All studies and registries of acute coronary syndromes show that the use of coronary angiography is significantly lower in women than in men. A coronary angiography was done in 53% of women compared to 59.3% of men in the GUSTO IIB study. It was found that the incidence of coronary arteries without significant lesions was approximately double in women compared to men,⁷ regardless of presenting ST-segment elevation infarction, non-ST-segment elevation infarction or unstable angina. Nevertheless, the absolute percentage of normal coronary arteries was much higher in the latter category than in the others in both sexes. In the DESCARTES⁴³ registry cardiac catheterization was done in 41.4% of the patients; of the 1234 participating men, 45.6% were catheterized vs 33.2% of the participating women ($P<.000$). However, as in the GUSTO IIB study, a greater percentage of women did not have significant coronary lesions compared to men (29.4% vs 12.3%; $P<.001$). Data from the recently published CURE study also demonstrates less use of invasive procedures in women than in men (47.6% vs 60.5%; $P=.0001$), which did not result in increased mortality, reinfarction, or stroke, but did involve a greater incidence of refractory angina in the women and the

need for readmission for angina during follow-up.⁵⁵ Although it could be argued that catheterization was less used in women due to the lower incidence of coronary lesions, this is not strictly true, because when the population was stratified according to the TIMI risk score in the CURE study, the women in the high-risk group underwent catheterization significantly less frequently than men (38.1% vs 45.5%; $P<.001$), and in this high-risk group the percentage of men and women with nonsignificant lesions was similar (59.6% vs 60.8%; $P=.68$).

These results reinforce the need to stratify the patients according to risk and employ the diagnostic techniques and treatment appropriate to the severity of the clinical picture, regardless of the sex of the patient.

Percutaneous Coronary Intervention

Lansky et al^{52,57} analyzed the results of hospital and long-term mortality in men and women undergoing elective percutaneous coronary intervention; the worst prognosis in the acute phase in women seems to involve a cluster of factors, such as advanced age, smaller body surface and other comorbidities. There seem to be no differences regarding long-term mortality. Nevertheless, women have between 1.5 to 4 times more probability of presenting vascular access complications; in this context, the importance of heparin dosage has already been discussed. The increase in the incidence of restenosis and the need for new revascularization in women has a direct relation to confounding factors, such as the greater incidence of diabetes in women or smaller caliber arteries in relation to smaller body surface.⁵⁷ Drug-eluting stents have reduced restenosis, the need for new revascularization and major cardiovascular events similarly in both men and women.⁵²

It has been shown that an initial invasive strategy combined with glycoprotein IIb/IIIa antagonists leads to a better prognosis in high-risk patients with non-ST-elevation acute coronary syndrome, and thus is recommended in the clinical practice guidelines. However, it is interesting to note that, in women, the FRISC II study did not show any difference regarding death or reinfarction at 1 year between the invasive strategy (average of 7 days) compared to conservative treatment with benefit (12.4% vs 10.5%).⁵⁸ In contrast, the TACTICS-TIMI study,¹⁸ where all patients received tirofiban and 34% of the population were women, demonstrated a significant reduction in mortality and reinfarction in women, as well as significant reductions in death, reinfarction and rehospitalization in women at high risk.⁵⁹ Thus, there are sufficient data to recommend an initial invasive strategy combined with glycoprotein IIb/IIIa antagonists in women with high-risk acute coronary syndrome.

Prognosis in Acute Coronary Syndrome

The GUSTO IIB study reported that women have a greater percentage of complications during admission and greater 30-day mortality (6% vs 4%; $P<.001$), but without differences in the percentage of reinfarction at 30 days. This study also demonstrated that there was an interaction between mortality and presentation of acute coronary syndrome; thus, women who presented with ST-segment elevation infarction, after adjusting for other covariates, had increased mortality compared to men (odds ratio [OR]=1.27; 95% confidence interval [CI], 0.98-1.63; $P=.07$). However, those presenting with unstable angina had a better prognosis (OR=0.65; 95% CI, 0.49-0.87; $P=.003$). Furthermore, they had fewer reinfarctions during follow-up and, as mentioned, they also had less incidence of coronary lesions.⁷ The CRUSADE registry also found that women with non-ST-segment coronary syndrome had greater crude hospital mortality than men (5.6% vs 4.3%), with a greater percentage of reinfarction (4% vs 3.5%) and heart failure (12.1% vs 8.8%), although these differences disappeared after adjustment.⁴⁹

Acute mortality following ST-segment elevation infarction is greater in women than in men, even after adjusting for age and comorbidity, and is probably due to greater disease severity. These results have been reported by several research groups⁶⁰ and have also been obtained in several Spanish registries, such as REGICOR,⁶¹ RESCATE,⁴⁵ and PRIAMHO II,⁴⁴ and have not changed in the last decade.

CONCLUSIONS

Ischemic heart disease in women has specific characteristics, some of which are still poorly identified. Fewer invasive studies are done in women and they usually undergo fewer diagnostic tests and receive less pharmacological and interventional treatments. More studies are needed to demonstrate the benefit of different therapies and treatment strategies in the female population.

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