

## Cardiovascular Diseases in Women (I)

**Cardiovascular Diseases in Women. Why Now?**Fernando Alfonso,<sup>a</sup> Javier Bermejo,<sup>b</sup> and Javier Segovia<sup>b</sup><sup>a</sup>Chief Editor. <sup>b</sup>Associate Editor. REVISTA ESPAÑOLA DE CARDIOLOGÍA.

In this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA we begin a new series entitled “Cardiovascular Diseases in Women” as part of the “Update” section. Why have we chosen this subject for 2006? In this introduction we review some alarming statistics and the most representative data on cardiovascular disease (CVD) in women in order to highlight this pressing issue.

**SOME EPIDEMIOLOGICAL DATA**

Cardiovascular disease is the most frequent cause of death in women in developed countries.<sup>1-4</sup> In fact, CVD mortality in women already surpasses that caused by the next seven combined causes of death and also deaths caused by all the malignant neoplasms together.<sup>1-4</sup> Recent data from the United States show that the absolute number of women who die from CVD is already greater than men.<sup>1-4</sup> The staggering figure of one death every minute is unforgettable, especially if we take into account that CVD can, to a great extent, be prevented. Most of these deaths are caused by coronary heart disease which often presents in its sudden form.<sup>1-4</sup> Although death from ischemic heart disease has decreased in males, its incidence remains stable in women.<sup>1-4</sup> Recent European data have confirmed that CVD is not only the leading cause of death in women in our socioeconomic setting, but also that its impact on total mortality is higher in women than in men.<sup>5</sup>

Section Sponsored by the Dr Esteve Laboratory

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**AWARENESS OF THE PROBLEM AND STRATEGIES FOR CHANGE**

The first prevention guidelines specific to women were published in 1999<sup>2</sup> and implemented recently.<sup>3</sup> However, awareness of the magnitude and severity of this problem in our society has been very limited, not only among women, but even among their own physicians and, especially, in the mass media. This point is crucial, as most women cite the mass media as their main source of information.<sup>2-4</sup> To date, campaigns designed to make information more available have only had modest results. Thus, whereas less than a third of women interviewed in 1997 were aware that CVD was the leading cause of death in the female population, this figure rose to 46% of respondents in 2003.<sup>4</sup> Thus, this shows a serious gap between perceived risk and real risk. This situation has led to an underuse in women of the diagnostic techniques currently available and indications for therapeutic strategies of proven efficacy.<sup>6</sup>

Hopefully, initiatives such as the “Go Red for Women” campaign of the American Heart Association ([www.americanheart.org](http://www.americanheart.org)), “Women at Heart” campaign of the European Society of Cardiology ([www.escardio.org/initiatives/womenheart](http://www.escardio.org/initiatives/womenheart)) and the creation within the Spanish Society of Cardiology of a specific Cardiovascular Disease in Women Working Group<sup>7</sup> will contribute to improving the current situation. The importance of the problem also clearly justifies the present “Update” of the REVISTA ESPAÑOLA DE CARDIOLOGÍA.

Women have been poorly represented in most clinical trials or registries devoted to CVD. Thus, a policy has recently been adopted to promote the inclusion of women in clinical trials.<sup>8,9</sup> The absence of studies on elderly women who have a higher prevalence of CVD is especially troubling. Thus, therapeutic guidelines should tell us when it is reasonable to extrapolate the data derived from predominantly male population studies to the female population (generalizability index =1) and when we should be especially cautious when making these assumptions (generalizability index =3).<sup>2-4,8,9</sup> Furthermore, any randomized study exclusively focused on women should be carefully assessed

regarding its justification. In the same line, some recent editorial initiatives have been adopted by many cardiovascular journals which ask for the data and results of the female population included in each study to be presented explicitly and in detail (HEART Group).<sup>10</sup>

### Women and Ischemic Heart Disease

Ischemic heart disease will be the subject most frequently discussed in this Update. From the standpoint of prevention, the dichotomous concept of CVD (present or absent) has currently shifted to the study of CVD risk as a continuous spectrum.<sup>2-4</sup> In the therapeutic context, many specific aspects have to be taken into account in women. Thus, class III recommendations, both for hormone replacement therapy and antioxidant supplements, are especially helpful.<sup>4</sup> Treatment with aspirin in women at low risk is also a class III recommendation.<sup>4</sup> In this sense, we should recall the recent interesting debate that has called into question the usefulness of aspirin in primary prevention in women,<sup>11</sup> whereas the beneficial effects of this drug on the male population are better established.

The lower prevalence of coronary heart disease in women (compared to men of the same age) has presented a continuous challenge regarding non-invasive diagnostic techniques due to the increasing numbers of false positives (Bayes theorem).<sup>12</sup> There is a time-lag of 10-15 years in premenopausal women in relation to the incidence of coronary disease compared to men, but it becomes similar for both sexes in the seventh decade of life.<sup>2-4</sup> Thus, the presence of classical risk factors and typical symptoms is of great help in measuring risk. Besides the importance of assessing risk with different classic scales (Framingham), we also know now that we should consider as high-risk all women with previous CVD, diabetes, or kidney failure.<sup>2-4</sup> Thus, in a well-selected population, the results of non-invasive tests will produce greater variations between the pretest and posttest probabilities, moving us closer to a more positive scenario. However, the striking underrepresentation of women in many of these studies brings even more into question how the results are applied. Interesting "consensus documents" have recently been prepared regarding the use of different non-invasive diagnostic methods in the female population.<sup>12</sup> The diagnostic cost-effectiveness of the exercise stress test, echocardiography stress test, and the use of radioactive isotopes has been well established. More current data hint at the possible usefulness of computerized tomography, magnetic resonance imaging, and the direct measurement of carotid artery thickness in women at intermediate risk.<sup>12</sup>

The WISE<sup>9</sup> and CRUSADE<sup>6</sup> studies have provided important data on understanding established ischemic heart disease in women. Women with non-ST segment

elevation acute coronary syndrome at high-risk are older and more frequently present diabetes and hypertension. Women receive the drugs recommended for this syndrome less frequently (including aspirin, heparin, glycoprotein IIb-IIIa inhibitors, angiotensin-converting enzyme inhibitors, and statins) and diagnostic catheterization and coronary revascularization procedures<sup>6</sup> are prescribed less often. Above all, due to the more unfavorable characteristics, adverse hospital events (death, reinfarction, heart attack, stroke, and hemorrhage) are also more frequent in women. However, women with acute coronary syndrome are checked by a cardiologist less frequently.<sup>6</sup>

The existence of a gender bias regarding coronary angiography has been demonstrated in multiple studies during the past decade.<sup>13</sup> We should recall here that just one-third of all percutaneous interventions are done in women.<sup>13</sup> Some works have even questioned the efficacy of an initially invasive strategy (FRISC II, RITA3)<sup>13,14</sup> and the use glycoprotein IIb-IIIa therapy<sup>15</sup> in women with acute coronary syndrome. Furthermore, it is a thoroughly recognized fact that, after an acute myocardial infarction, prognosis is significantly worse in women, who present a greater frequency of reinfarction, heart failure, cardiogenic shock and cardiac rupture, and have greater hospital and late mortality.<sup>16,17</sup> However, women with acute myocardial infarction less frequently undergo reperfusion and revascularization procedures.<sup>13</sup> It has been pointed out that, in women, thrombolysis could be less effective and could be associated with greater risk of bleeding.<sup>18</sup> On the other hand, we know that the results of the different modalities of coronary revascularization are significantly worse in women, and that this event does not seem to be accounted for only by the smaller size of the coronary vessels. Although age and adverse cardiovascular and systemic profile in women with coronary heart disease clearly play a very important role in these results, some studies have demonstrated that female sex per se constitutes an independent predictor of morbidity and mortality.<sup>13,19-21</sup> Paradoxically, despite their worse baseline characteristics, both the restenosis rate and long-term clinical evolution are similar to those found in the male population.<sup>20,21</sup> Very recent data from a wide series of patients also confirm the worse outcomes obtained after coronary revascularization surgery in women, even after adjusting for multiple confounding factors.<sup>22</sup>

### Implications of Gender on Other Cardiovascular Diseases

A very similar situation has been observed regarding stroke which is also much more frequent in women. Although women have some less favorable baseline characteristics and greater mortality and residual disability after a cerebrovascular episode, they less frequently

undergo diagnostic techniques and appropriate therapeutic interventions.<sup>23</sup> It is important also to bear in mind that the efficacy of aspirin in women for primary prevention of stroke has not been demonstrated in men.<sup>11</sup>

The influence of female sex on the prevalence and characteristics of rheumatic valvular disease and of other valvular alterations, such as mitral valve prolapse, is already well-known. However, its involvement in degenerative valvulopathy has aroused interest more recently. Thus, in degenerative aortic stenosis, both the severity of calcification and the degree of hypertrophy and left ventricular function disorder are different in the female population.<sup>24-27</sup>

The peculiarities and prognostic implications of heart failure in women have also been well analyzed, both in patients with preserved systolic function and depressed ejection fraction.<sup>28,29</sup> In the first place, an appropriate clinical diagnosis of heart failure is achieved less frequently in women. Different studies have shown that women with heart failure are older, have greater comorbidity, and that hypertension is the most frequent causal factor.<sup>29</sup> Furthermore, correct assessment of the state of ventricular function is carried out less frequently in women and they receive angiotensin-converting enzyme inhibitors less often. Response to pharmacological treatment can be different in women and caution is especially required regarding indications for digoxin.<sup>8</sup> It is also well known that the presence of heart failure with preserved systolic function (previously labeled as diastolic) is much more common in women.<sup>28,29</sup> The lower frequency with which women with heart failure are checked by a cardiologist probably accounts for much of this data.<sup>28</sup> The lower use of suitable therapeutic measures in women with heart failure in our context has recently been confirmed in the EuroHeart Survey.<sup>30</sup>

Different studies (including the Framingham study) have shown that the secondary forms of ventricular hypertrophy are associated with a greater risk of cardiovascular events in women.<sup>31</sup> The role of female sex in hypertrophic cardiomyopathy has also been described recently.<sup>31</sup> The under-representation of women in most studies addressing this issue is clear, although, due to the way this entity is genetically passed on, its prevalence should necessarily be similar in both sexes. Women with hypertrophic cardiomyopathy are older and more symptomatic than men, which implies—once again—that diagnosis is carried out with more delay. In women, ventricular diameters are smaller, while intraventricular gradients are more frequent. Finally, death due to heart attack or stroke occurs more often in women than in men with this disease.<sup>31</sup>

Cardiac arrhythmias deserve being treated as a separate issue. Women have a higher baseline heart rate and a lower incidence of sudden death.<sup>32,33</sup>

Furthermore, in sudden-death survivors, it is relatively frequent to find structurally normal hearts and an absence of coronary heart disease.<sup>32,33</sup> Prolonged QT interval and torsades of pointes<sup>8</sup> are more frequent in women. However, the prevalence of atrial fibrillation, preexcitation, and ventricular tachycardia are more common in men. Again, there are important differential characteristics between women with supraventricular arrhythmias and those with ventricular arrhythmias that must be understood. For example, in women it is normal to attribute symptoms of supraventricular tachycardia to anxiety.<sup>34</sup> Finally, although ablation procedures seem to be equally effective in women and men, women are treated with this technique much later (greater duration of symptoms, higher numbers of proven antiarrhythmic drugs, and more severe symptoms).<sup>35</sup>

## FUTURE PROSPECTS

The “Go Red for Women” and “Women at Heart” initiatives mentioned above will help to radically change our knowledge and, thus, the approach to and treatment of CVD in women. In the United States, some public agencies that support research trials have decided to only finance those studies in which a preestablished minimum number of women are represented. In Europe, detailed data from the EuroHeart Survey will soon be available which specifically analyzed the effect of gender on many relevant diseases (acute coronary syndromes, diabetes, heart failure and atrial fibrillation).

Finally, biomedical journal editors intend to encourage all authors to present data specific to the female subpopulation in their studies.<sup>10</sup> From now on, it is especially important to highlight whether or not being female has an influence on the primary endpoints of the study and on complications or adverse effects. All these new data will make it more difficult to justify a still widespread attitude involving gender bias in the diagnosis and treatment of women with CVD. Clearly, these measures will help to improve the prognosis of women with CVD.

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