



# Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology

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Cardiovascular diseases (CVD) are the leading cause of mortality both in men and women. In Europe, about 55% of all females' deaths are caused by CVD, especially coronary heart disease and stroke. Unfortunately, however, the risk of heart disease in women is underestimated because of the perception that women are 'protected' against ischaemic heart disease. What is not fully understood is that women during the fertile age have a lower risk of cardiac events, but this protection fades after menopause thus leaving women with untreated risk factors vulnerable to develop myocardial infarction, heart failure, and sudden cardiac death. Furthermore, clinical manifestations of ischaemic heart disease in women may be different from those commonly observed in males and this factor may account for under-recognition of the disease. The European Society of Cardiology has recently initiated an extensive 'Women at heart' program to coordinate research and educational initiatives on CVD in women. A Policy Conference on CVD in Women was one of the first steps in the development of this program. The objective of the conference was to collect the opinion of experts in the field coming from the European Society of Cardiology member countries to: (1) summarize the state-of-the-art from an European perspective; (2) to identify the scientific gaps on CVD in women; and (3) to delineate the strategies for changing the misperception of CVD in women, improving risk stratification, diagnosis, and therapy from a gender perspective and increasing women representation in clinical trials. The Policy Conference has provided the opportunity to review and comment on the current status of knowledge on CVD in women and to prioritize the actions needed to advance this area of knowledge in cardiology. In the preparation of this document we intend to provide the medical community and the stakeholders of this field with an overview of the more critical aspects that have emerged during the discussion. We also propose some immediate actions that should be undertaken with the hope that synergic activities will be implemented at European level with the support of national health care authorities.

## Cardiovascular diseases in women: the problem

### The need for a Policy Conference on cardiovascular diseases in women

Cardiovascular diseases (CVD) are the leading cause of mortality both in men and women.<sup>1</sup> In Europe, about 55% of all females' death are caused by CVD, especially coronary heart disease (CHD) and stroke.<sup>1</sup> Unfortunately, however, the risk of heart disease in women is underestimated because of the perception that women are 'protected' against ischaemic heart disease. What is not fully understood is that women during the fertile age have a lower risk of

cardiac events, but this protection fades after menopause thus leaving women with untreated risk factors vulnerable to develop myocardial infarction, heart failure, and sudden cardiac death. Furthermore, clinical manifestations of ischaemic heart disease in women may be different from those commonly observed in males and this factor may account for under-recognition of the disease.

The European Society of Cardiology has recently initiated an extensive 'Women at heart' program to coordinate research and educational initiatives on CVDs in women. A Policy Conference on Cardiovascular Diseases in Women was one of the first steps in the development of this program. The objective of the conference was to collect the opinion of experts in the field coming from the European Society of Cardiology member countries to (i) summarize the state-of-the-art from an European perspective; (ii) to identify the scientific gaps on CVDs in women; and (iii) to delineate the

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strategies for changing the misperception of CVDs in women, improving risk stratification, diagnosis, and therapy from a gender perspective and increasing women representation in clinical trials. Results of the discussion are summarized in the present document.

### Epidemiology of CVDs in women

CVDs represent the leading cause of death both for men and women as indicated by the data released in 2004 by the World Health Organization highlighting that, in Europe, CVDs account for 43% of deaths in men and 55% in women.<sup>1</sup> When the different components of CVDs are considered (Figure 1), CHD represents 21% of deaths in men and 23% in women, whereas stroke is a relatively more frequent cause of death in women than in men (18 and 11%, respectively), as well as the other CVDs (15% in women and 11% in men). As a consequence, stroke represents the third commonest cause of death in men and the second in women: as a comparison it is interesting to report that breast cancer accounts for 3% of all deaths.

It has been clearly shown that the prevalence and the incidence of CVDs among both men and women increase with age.<sup>2</sup> Furthermore, as life expectancy increases and it does so particularly in women, the proportion of women with CVDs shows an important rise. Specifically, in younger age groups, the prevalence of CHD is lower in women when compared with men, but the gender difference narrows at older ages. The prevalence of stroke is slightly higher in men than in women, irrespective of age.

Age-adjusted mortality for CVDs has steadily declined in the last 40 years in the population of Western countries. However, when the trends of mortality rate are analysed by gender, a decline of lesser magnitude is observed in women.

The temporal trend of the incidence of CVD shows a decline in men but a rise in women. This is mostly because of a decrease in myocardial infarction incidence in younger men with a concomitant increase in older women.<sup>3</sup>

*CVDs are a major cause of mortality and morbidity for women and the burden of the disease is increasing. This unequivocal epidemiological observation should be taken into account for health promotion policies.*

### Misperception of the importance of CVDs as a major cause of morbidity and mortality among women

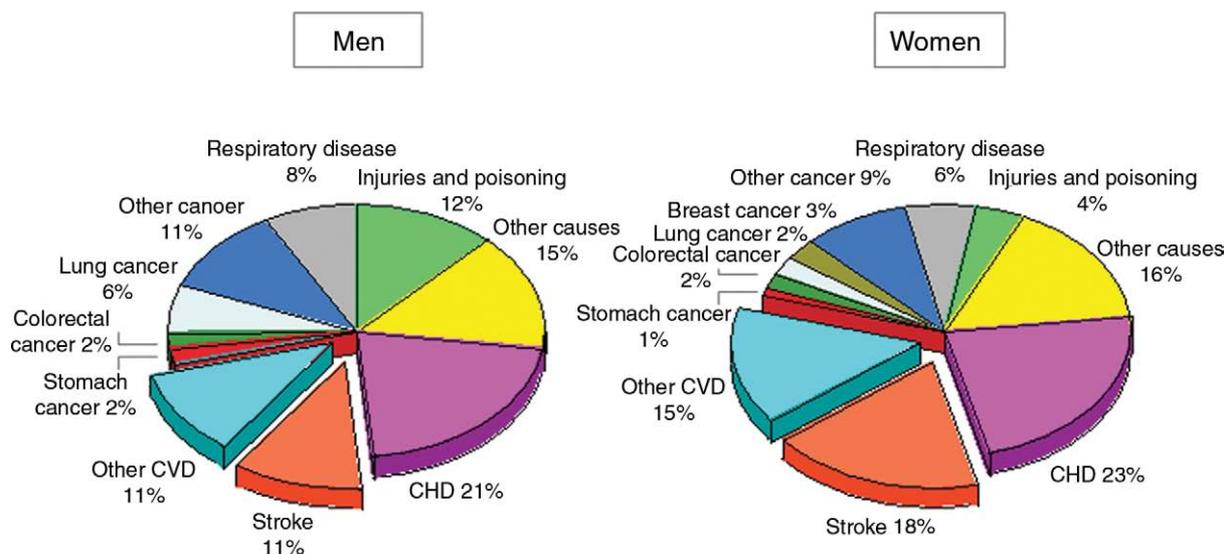
Recent surveys have shown that, although the awareness among women that heart disease is the leading cause of mortality is increasing, only a small percentage of women believe that heart disease and stroke constitute the greatest threat to their health.<sup>4</sup> In fact, although breast cancer claims nearly one-tenth of females' lives as compared with CVD, it is often reported by the media as the leading cause of morbidity and mortality for females. This misperception is one of the barriers to the systematic reduction of cardiovascular risk factors among women.

*A strong action should be taken in order to increase the awareness of women on the importance of preventing CVD. This has implications for the education of both the general population and the medical and scientific community.*

### Possible gender difference in the response to therapy and under-representation of women in cardiovascular clinical trials

It has been suggested that there is a gender difference in the clinical manifestation of CVDs and in the response to therapy.<sup>5</sup> The understanding of these differences may improve the clinical management of CVDs and possible

Causes of Death by Gender in the European Countries



World Health Organization (2004)

Figure 1 Causes of death in Europe. WHO, World Health Organization.

new gender-specific diagnostic and therapeutic options may be developed.

The response to therapy may differ in women when compared with men because of different endogenous hormone levels, a lower body weight, and a higher proportion of fat.<sup>6</sup> Gender differences in enzyme activities involved in drug metabolism as well as a lower glomerular filtration rate which influences drug elimination have been demonstrated.<sup>7</sup>

The most important example that has highlighted the importance of addressing gender-specific issues in response to cardiovascular therapies comes from the evaluation of aspirin effect in primary prevention of myocardial infarction and stroke. A meta-analysis that included data from the recent Women's Health Study conducted only in females, and from trials involving a majority of men with no history of heart disease indicates that aspirin therapy reduces the risk of stroke but does not affect the occurrence of myocardial infarction in women.<sup>8</sup> In contrast, in men, aspirin significantly reduces the risk of myocardial infarction with a non-significant increase in the risk of stroke. The reasons of these different effects of aspirin in men and women have not been clarified yet but these findings may have important clinical implications and stress the importance of an adequate representation of women in clinical trials.

There is therefore a common agreement that gender-related differences in response to therapy should be addressed in a more systematic fashion. Clinical trials should be designed and powered to provide conclusive answers to questions related to gender differences. Gender-related endpoints should be included in trials protocols, thus overcoming the limitations of *post hoc* analyses. It seems appropriate to use *post hoc* analyses to generate hypotheses that should be tested in future trials. An example of the risk of relying on *post hoc* analyses comes from the DEFINITE study,<sup>9</sup> where initial data suggested a lack of benefit of ICD to prevent total mortality in women who represented 29% of the population. Further evaluation of data clarified that women had had an excess of death because of non-arrhythmic causes and that, in fact, the ICD was effective in preventing lethal arrhythmic episodes.

When investigating gender issues in clinical trials, two strategies may be used for designing a study: the first is to enrol both males and females, ensuring that the number of patients enrolled for each gender is adequate to reach statistically significant results. The second option is to follow the example of the Women's Health Study<sup>8</sup> and enrol only women. There are pros and cons to both approaches: it seems appropriate to conclude that the choice of the best approach to be taken should be tailored to the specific question being addressed. If the fundamental question is whether differences exist between males and females, it may be reasonable to design a trial that enrolls patients of both genders but in which the number of participants to be enrolled is calculated separately for each gender. Alternatively, if the focus of the investigation is to find out whether females respond to a given treatment or not, it may be more effective to design a trial that enrolls only women.

*The lack of conclusive data on the magnitude of gender differences in response to cardiovascular therapies should stimulate basic and clinical research to advance the knowledge on this topic. Although non-pre-specified, post hoc,*

*subgroup analysis by gender for already completed clinical trials with adequate power and representation of women may help to explore the issue and may contribute to the hypothesis generating process, it is clear that targeted clinical trials are needed. As a consequence, it is recommended that based on the specific question addressed, clinical trials enrolling only female patients or clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis will be conducted.*

## Risk of CVDs from a gender perspective

### Prevalence of risk factors and their control in men and women

The identification of risk factors and their control through preventive measures has contributed to a reduction in CVDs and related mortality in both men and women. However, the prevalence of risk factors in both men and women is still high and further efforts in the area of primary and secondary prevention should be made.

It has been shown that the prevalence of risk factors in various age groups is different in women when compared with men. Age is an important risk factor for both genders, but women are on average 10 years older than their male counterparts when they develop CVD.<sup>2</sup> This is probably related to the different hormone levels in the post-menopausal years.

Also the age at which the risk factors appear, differs between men and women. More women, than men, develop hypertension as they get older, particularly women over 45 years.<sup>10</sup> In older women, isolated systolic hypertension is the more common form of hypertension.<sup>11</sup> Control of any form of hypertension has been demonstrated to reduce the risk of coronary artery disease and stroke in both genders, as shown by the large clinical trials with a fair representation of women.<sup>12,13</sup>

Tobacco use represents an important risk factor for both men and women. Although the prevalence of smokers is still slightly higher in men than in women, the decline in tobacco use among women is less evident than in men.<sup>14</sup> In young women who smoke, the use of oral contraceptives further increases the risk.<sup>15</sup>

Total cholesterol levels in women peak between 55 and 65 years of age, about a decade later than in men.<sup>16</sup> In both genders, elevated cholesterol levels are associated with increased risk for cardiovascular events. The use of lipid-lowering agents, especially statins, reduces the risk in both men and women, regardless of the baseline cholesterol level.<sup>17</sup> However, there is a larger proportion of women at high risk who are not effectively treated and who do not reach the LDL cholesterol levels specified by the guidelines.<sup>18</sup>

Prevalence of diabetes is increasing in both men and women.<sup>19</sup> The risk of CHD mortality associated with diabetes appears to be higher in women than in men. However, when mortality is adjusted for the other cardiovascular risk factors the gender difference is no longer present.<sup>20</sup>

Obesity is also more prevalent in men until 45 years and in women after that age.<sup>19</sup> The risk of cardiovascular events is increased especially in subjects with central obesity,<sup>21</sup> because of the concomitance of other risk factors or co-morbidities, which are very often present in obese

women. In fact, the metabolic syndrome, defined by the presence of three or more of risk factors, which include central obesity, is more prevalent in women than in men with CHD.<sup>18</sup>

Women are less likely than men to identify their risk factors (body mass index, smoking, blood pressure, cholesterol) and this may affect the implementation of more aggressive management for women at higher risk for cardiovascular events.<sup>22</sup>

Strategies for the control of risk factors have been outlined in the Third Joint European Society's Task Force on Cardiovascular Disease Prevention in Clinical Practice.<sup>23</sup> These guidelines differ from earlier ones in stressing the need to prevent all atherosclerotic CVD rather than just CHD, in the use of a new cardiovascular risk prediction system [Systematic Coronary Risk Evaluation (SCORE)],<sup>24</sup> and in the definition of explicit clinical priorities.

### Cardiovascular risk stratification from a gender perspective

The Third Joint Task Force recommendations on CVD prevention<sup>23</sup> specifically stress the importance of total risk evaluation in both men and women. This is because atherosclerotic CVD is multifactorial in origin, and the causative risk factors interact to produce total risks that may be greater than the sum of the components.

The SCORE system<sup>24</sup> is recommended as a simple way to estimate the risk of dying of CVD over the next decade. It is based on 12 European Cohort Studies, comprising 122 705 men and 93 208 women. The 10-year absolute CVD risk for men and women living in the high and low risk (mostly the Mediterranean basin) areas of Europe can be immediately estimated from the SCORE charts (Figures 2 and 3).

Younger women all appear to be at very low absolute risk. Although this is true, this may conceal very large relative risks—for example, nobody is really at zero risk and the difference between a risk of 0.1 and 1% is 10-fold. For this reason, it is suggested to extrapolate risk to age 60 to determine what the risk will be if the present risk status continues until that age. However, more innovative methods of expressing large relative risks concealed within small absolute risks are needed.

The charts appear to indicate that women are at lower risk than men. However, the only difference is that their risk is delayed by 10 years. For example, inspection of the high-risk chart (Figure 2) shows that a 60-year-old woman has an almost identical risk to a 50-year-old man. Thus, women enjoy a 10-year advantage in risk, but nevertheless are not overall at lower risk than men.

*Both the absolute risk and relative risk should be estimated, as women at low absolute risk may carry a high relative risk. Risk factors that are particularly important for women, i.e. diabetes and obesity, should be taken into*

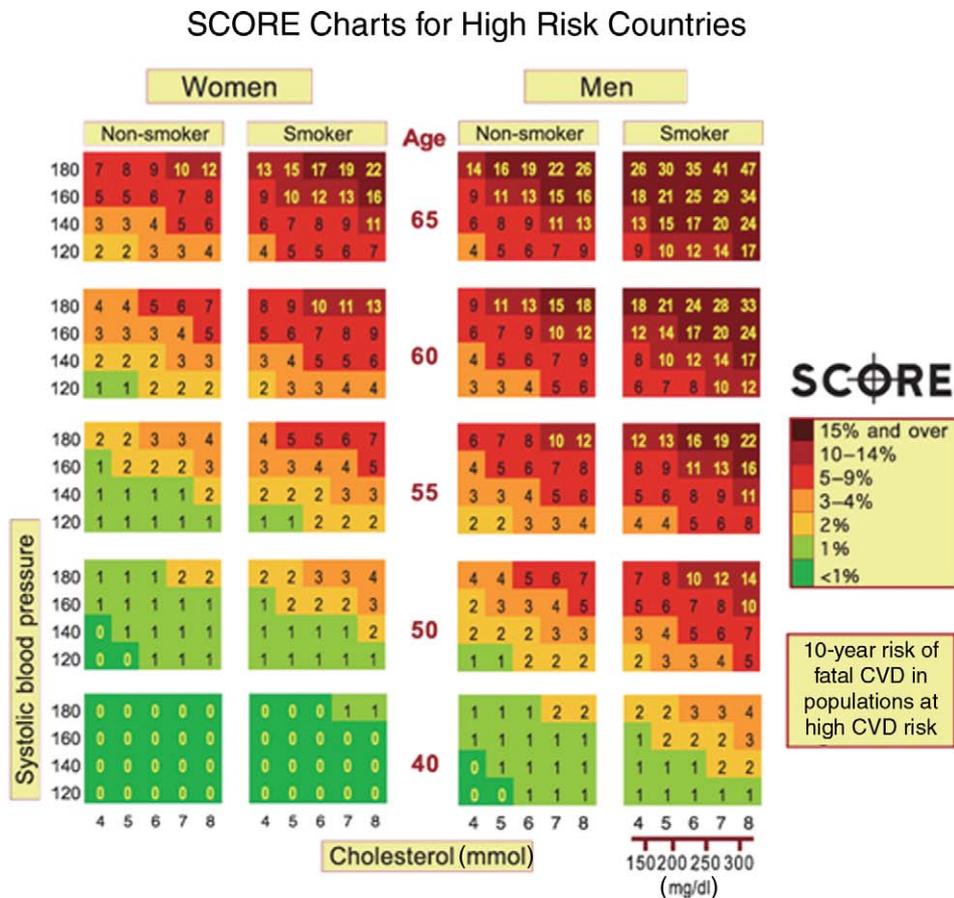


Figure 2 SCORE charts for high-risk countries.

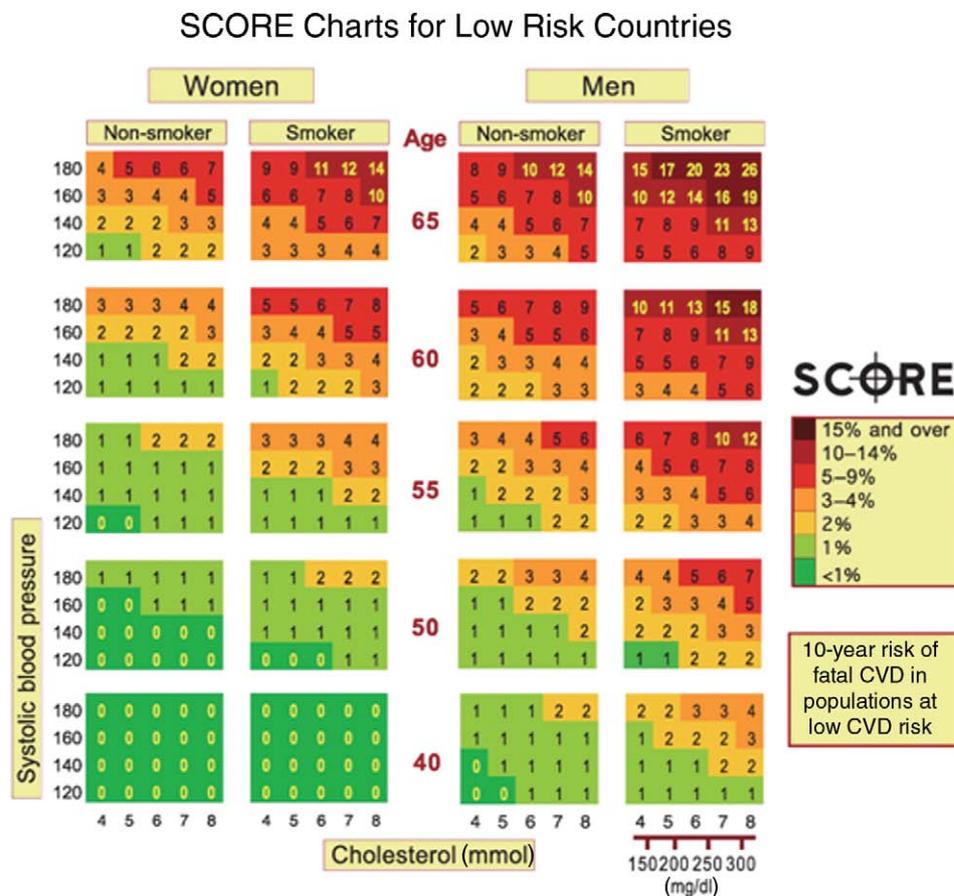


Figure 3 SCORE charts for low-risk countries.

account. Risk should be extrapolated to a higher age in women (70 years instead of 60 years).

### Menopausal hormone therapy and cardiovascular risk

Menopausal hormone (replacement) therapy is presently used for the relief of menopausal symptoms and in some countries for the prevention of post-menopausal osteoporosis.<sup>25</sup> Hormone replacement therapy comprises oestrogen, with or without the addition of a progestin (a synthetic progestational hormone). Oestrogen is given on a continuous basis, by tablets, skin patches, skin gels, subcutaneous implants or intranasal sprays. Progestins can be given by tablets and skin patches, and locally by intra-uterine systems. Progesterone can be given by tablets, pessaries, and suppositories. The main action of progesterone and progestins is to prevent or reverse oestrogen-induced proliferation of endometrial tissue and thus progestins are not usually given to women who have undergone hysterectomy. Although the endometrial effects of the different progestins tend to be similar, their metabolic effects can be quite different.

Loss of ovarian hormones at the menopause has a widespread adverse impact on many cardiovascular risk factors. However, recent large clinical trials of essentially one form of hormone therapy—combined therapy of continuous equine estrogens (premarin) and medroxyprogesterone acetate (MPA) or continuous equine oestrogen (premarin)

alone—have not shown a benefit on cardiovascular risk.<sup>26–30</sup> Therefore, at the present time, hormone therapy is not recommended for post-menopausal women solely for cardioprotection.<sup>31</sup> It is also clear, however, that there are differences with regard to endpoints between the two large arms of the Women's Health Initiative (WHI) studies, which may suggest a detrimental effect not of the oestrogen used but rather of the progestin (MPA).<sup>27,29</sup> The failure of the clinical trials to show a benefit may be, in part, due to the selection of the population in terms of age, but may additionally be due to inappropriate hormone therapy regimens, in terms of dose and possibly type of steroids, being employed. A pattern of early harm followed by later benefit has emerged from these trials. It is plausible that transient adverse effects on thrombogenesis and vascular remodelling are responsible for the early harm, whereas beneficial effects on metabolic risk factors and arterial function are responsible for possible later benefit. Hormone therapy regimens vary considerably in their metabolic effects, and hence in their cardiovascular effects. Further research is required to define the ideal dose, type, route of administration, and duration of hormone therapy for maximum potential cardiovascular benefit.

For many women, the short-term relief of menopausal symptoms with hormone replacement therapy will likely be worth the small absolute increase in risk for heart disease or breast cancer. Because it is suggested that the risk of these complications increases with the duration of time hormone replacement therapy is used, the goal

should be to use hormone replacement therapy for the shortest period of time necessary to successfully treat menopausal symptoms.

*On the basis of the available evidence menopausal hormone therapy cannot be recommended for the prevention of CVDs. Further studies are necessary in order to assess benefits and risks of different dosages, route of administration, and duration of menopausal hormone therapy.*

## Gender differences in the diagnosis and treatment of CHD

Gender differences in the clinical manifestation of CHD have been demonstrated in several studies. Women have a greater tendency to present with atypical chest pain or to complain of abdominal pain, dyspnoea, nausea, and unexplained fatigue.<sup>32</sup> As women tend to have heart attacks later in life than men, they often have other diseases that can mask heart attack symptoms.<sup>33</sup> Furthermore, ischaemia may be more often silent in women<sup>34</sup> and the proportion of unrecognized myocardial infarction is greater in women than in men.<sup>35</sup> On the other hand, some diagnostic tests and procedures may not be as accurate in women, so physicians may avoid using them and a heart attack or stroke may not be detected in women until later, with more serious consequences.<sup>36</sup> Exercise stress testing, commonly used to diagnose ischaemic heart disease, may be less accurate in women:<sup>37,38</sup> in young women with a low likelihood of CHD, an exercise stress test may give a false positive result,<sup>39</sup> whereas in contrast, single-vessel CHD, which is more common in women than in men, may not be identified by a routine exercise stress test.<sup>40</sup>

*Gender differences in the manifestation and the time-course of CHD should be taken into consideration in the clinical practice. The analysis of the results of diagnostic tests should account for gender-related differences in their predictive value.*

## Angina

Although many population-based studies report the prevalence of stable angina to be at least as high in women as in men, investigation into the impact of gender on the diagnostic approach and treatment of stable angina has therefore been limited. The Euro Heart Survey of Stable Angina<sup>41</sup> is unique in assessing the impact of gender at multiple levels in the management of stable angina, from initial assessment to revascularization. In this European survey (conducted between 2002 and 2003) of patients presenting 'de novo' to cardiologists with stable angina, women accounted for 42% of the 3779 patients enrolled.

Women were significantly less likely to be referred for functional testing for ischaemia, in particular for exercise testing, less likely to receive angiography even after adjustment for the results of non-invasive tests, and were less likely to be referred for revascularization. Women were also less likely to receive secondary preventive therapies (aspirin or statin) at initial assessment. Among patients with angiographic confirmation of coronary disease during follow-up, women remained less likely than men to receive optimal secondary preventive therapy at 1 year. In the subgroup with confirmed coronary disease, female

gender was strongly associated with increased risk of death and myocardial infarction, independent of age and other predictors of adverse outcome.

*There is robust evidence that women with stable angina are both under-investigated and under-treated in contemporary practice. Further research is needed to elucidate the reasons for the adverse prognosis observed in women with stable angina and proven coronary disease.*

## Myocardial infarction and acute coronary syndromes

Gender differences in the manifestation of acute coronary syndromes (ACS), including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina have been demonstrated.<sup>42</sup> In the GUSTO-II ACS<sup>36</sup> study, involving more than 12 000 patients, women were older at presentation for ACS and had a higher prevalence of risk factors such as hypertension, diabetes, and hypercholesterolaemia. However, a larger proportion of women with unstable angina or non-ST-elevation myocardial infarction did not have significant large vessels CHD, suggesting a higher prevalence of microvascular endothelial dysfunction or non-stenotic atherosclerosis as shown by studies in which intravascular ultrasound examination was performed.<sup>43</sup> In the Euro Heart Survey of ACS<sup>44</sup> involving more than 10 000 patients, women under 65 years were more likely than men to present with unstable angina, and less likely to have ST-elevation myocardial infarction, whereas women and men over 65 years had a similar distribution of diagnoses at presentation. However, women over 65, with ST-elevation myocardial infarction were significantly less likely to receive reperfusion therapy. Among patients over 65 years women were also more likely to have heart failure at presentation and this may partially explain the higher in-hospital mortality in females.<sup>45</sup>

*The older age at presentation, the higher prevalence of risk factors, and the higher mortality in women with ACS should be taken into account in clinical management. New studies are necessary for the assessment of long-term prognosis in women with ACS and non-significant large vessels coronary stenosis.*

## Revascularization procedures in men and women

Gender differences in patients undergoing coronary revascularization procedures have been reported. Similar to ACS, more women than men who receive surgical or percutaneous revascularization have hypertension, diabetes mellitus, and hypercholesterolaemia.<sup>46</sup> Despite a higher prevalence of additional risk factors women undergoing by-pass surgery show a similar outcome than men.<sup>47</sup> It has been shown that women at cardiac catheterization have smaller coronary arteries<sup>48</sup> and that the vessel size influence device utilization for percutaneous revascularization with a lower use of endovascular stents.<sup>49</sup> The risk of adverse events during and after the procedures, including coronary dissection and peripheral local bleeding, is greater in women than in men. The success rate of percutaneous revascularization is similar in men and women,<sup>50</sup> as well as the effects of new anti-thrombotic agents as concomitant therapy<sup>51</sup> and the reduction in restenosis with the wider use of drug-eluting stents.<sup>52</sup> However, in-hospital mortality rate remains higher in women, but disappears after adjustment for risk

factors.<sup>53</sup> Also primary angioplasty during myocardial infarction has been shown to be beneficial in both men and women. However, the PAMI study showed that women had a higher 6-months mortality rate, re-infarction, and stroke.<sup>54</sup> Moreover, the CADILLAC study demonstrated that primary stenting with or without the glycoprotein IIb/IIIa inhibitor abciximab is superior to traditional angioplasty in both men and women.<sup>55</sup> Despite the improvement in outcome in both sexes the overall mortality in women with acute myocardial infarction undergoing primary stenting was higher than in men.

*The use of proven effective interventions for coronary revascularization should be promoted in women with coronary artery disease. Further effort is necessary for the improvement of devices particularly customized for the anatomy and physiology of female coronary arteries.*

## Gender differences in heart failure

Heart failure is the most common cause of hospital admission in both men and women. The overall prevalence of heart failure is similar in men and women. However, important gender differences in the manifestation of heart failure exist.<sup>56</sup> The prevalence of heart failure increases with age in both genders but men are diagnosed at younger age, whereas heart failure is more common among women older than 75 years.<sup>57</sup> As life expectancy is greater in women than in men, the proportion of older women with heart failure is higher than that of men and is expected to further increase in the near future.

Hypertension and CHD are the most common aetiological factors in heart failure for both genders, but hypertensive women appear to have a higher risk of developing heart failure than men.<sup>58</sup> Both the prevalence of diabetes and the risk of heart failure in diabetic patients are higher in women when compared with men even after adjusting for other risk factors.<sup>59</sup> Although CHD is less frequent in women with heart failure than in men, after myocardial infarction the risk of heart failure is higher in females.<sup>60</sup>

Women with heart failure tend to experience more symptoms than men and the number of hospitalizations is higher among women than among men.<sup>56,60</sup> These observations are partially explained by the older age at presentation of the disease. Despite the higher frequency of symptoms, clinical trials on therapeutic interventions and large databases have shown a better survival rate for women than for men with heart failure.<sup>61,62</sup>

It has been shown that women with heart failure more often have a preserved left ventricular function.<sup>63</sup> Recently, the Euro Heart Survey conducted in patients with heart failure, corroborated this finding.<sup>64</sup>

Gender-specific data on the response to therapy are scant and no gender-based difference in heart failure treatment is recommended by guidelines. However, a *post hoc* analysis of the DIG trial showed that women with heart failure who received digoxin had a higher mortality than those receiving placebo,<sup>65</sup> an effect that was not observed in men. The lower renal clearance of digoxin in women may have contributed to these effects on mortality, as a higher percentage of women had drug plasma levels above the therapeutic range.<sup>66</sup>

Data from the Euro Heart Survey on heart failure have shown that there are not important differences in the

treatment of patients with heart failure among European physicians.<sup>67</sup> The use of ACE-inhibitors, angiotensin receptor antagonists and beta-blockers is similar in men and women, whereas a smaller proportion of women receive spironolactone when compared with men.

The lack of evidence for gender differences in response to heart failure therapy is not limited to pharmacological therapies, but also extends to devices. The large clinical trials (MADIT II, COMPANION, and SCDHeFT) that have supported a Class I indication for the ICD in patients with heart failure<sup>68</sup> included, respectively, a mere 16, 23, and 31% of females.<sup>69-71</sup> Similarly, the indication of resynchronization therapy is based on data almost entirely obtained in men as, for example, CARE-HF enrolled only 26% of females.<sup>72</sup>

*The under-representation of women in clinical trials is particularly evident for studies that evaluated treatment options in heart failure patients. As a consequence there is a lack of evidence for gender differences in the response to heart failure therapy. A larger female representation in clinical trials on heart failure will also allow a better understanding of diastolic dysfunction, which is more prevalent in women.*

## Gender differences in the clinical manifestation and outcome of stroke

Stroke is a major cause of death in both men and women. It also represents the first cause of disability and the second cause of dementia with a tremendous impact on patients, their families, and the society. Gender differences in the clinical presentation and outcome of stroke have been suggested. It has been shown that gender differences in clinical management after an acute stroke exist.<sup>73</sup> A multi-center study conducted in seven European countries<sup>73</sup> showed that after an acute cerebrovascular event, brain imaging, Doppler examination, echocardiogram, and angiography were significantly less frequently performed in female than in male patients. The frequency of carotid surgery was also significantly lower in female patients.

## Neurological impairment and disability after stroke in men and women

The degree of neurological impairment and that of disability at hospital discharge and at 1 year were evaluated in consecutive patients admitted for an acute cerebrovascular event.<sup>74</sup> Neurological impairment, expressed with the NIH Stroke Scale, was greater in women than in men as well as the degree of disability at hospital discharge, expressed by the Barthel Index. At 1 year, more men than women were completely independent. Severe disability was more frequent in women than in men. These gender differences are only partially explained by the older age of women at the time of stroke, since they persist when the analysis is performed in stroke patients older than 75 years.

*Stroke outcome is worse in women than in men, regardless the older age of women at presentation.*

## Atrial fibrillation and risk of stroke in men and women

At variance with myocardial infarction, stroke is a heterogeneous disease because different causes are involved in

its genesis. Among the pathogenetic mechanisms of stroke, embolism from the heart, which is usually associated with larger infarcts, accounts for a higher percentage of strokes in women than in men. This observation may partially explain the greater degree of disability in women. Atrial fibrillation, the most important cause of cardioembolism, is indeed more frequent in women who suffered a stroke when compared with their male counterparts.<sup>74</sup> The EURO Heart Survey on atrial fibrillation has shown that women have higher values of CHADS<sub>2</sub> score, a chart that expresses the risk of stroke on the basis of risk factors (CHD, heart failure, age, diabetes, and previous cerebrovascular event) associated with atrial fibrillation.<sup>75</sup> Indeed, large observational studies of atrial fibrillation have shown a higher incidence of stroke in women when compared with men. In the ATRIA study<sup>76</sup> including approximately 15 000 patients with atrial fibrillation the risk for ischemic stroke was greater in women than in men (RR 1.6; 95% CI 1.3–1.9) after adjustment for age and the presence of other risk factors and it was even higher in women older than 75 years. However, despite a larger percentage of women at higher risk for stroke and a similar beneficial effect of anticoagulant therapy,<sup>76</sup> a smaller percentage of women with atrial fibrillation than men prior to an acute cerebrovascular event were treated with oral anticoagulants.<sup>74</sup>

*A higher prevalence of atrial fibrillation and cardioembolic stroke in women may partially explain the differences in outcome after stroke. Despite the higher risk of stroke and a similar efficacy of therapy, women with atrial fibrillation prior to acute stroke do not receive adequate anti-thrombotic therapy.*

### Acute stroke therapy and gender

Thrombolytic therapy for acute ischaemic stroke has been recently approved in Europe. In a recent meta-analysis, women have been shown to benefit more than men from this therapy.<sup>77</sup> The beneficial effect of thrombolytic therapy is particularly evident when administered early after the onset of symptoms. However, despite the greater efficacy of thrombolytic therapy, the percentage of women who do not receive tPA after acute ischaemic stroke is higher when compared with men.<sup>78</sup> Thrombolytic therapy after stroke should be administered within the first 3–6 h after the onset of symptoms, as after this period of time the risk of bleedings outweighs the benefit of treatment. The percentage of women who reach the hospital within 3 or 6 h is lower than that of men and this observation may partially explain the under-treatment of women with thrombolytic therapy.<sup>74</sup>

*Despite a worse outcome after stroke and a greater efficacy of thrombolytic therapy, women often do not receive this treatment, mostly because of an excessive delay in hospital arrival after the onset of symptoms.*

### Cost-effectiveness and allocation of resources for reducing the burden of CVDs in women

#### Cost of CVDs by gender

A significant proportion of health care expenditure is related to CVD. It has been calculated that in the USA, direct health care costs for CVD in 2004 were US\$ 227 billion and indirect costs 142 billion. A Swedish estimate for the same year

indicates direct costs of SEK 28 billion and indirect costs of 30 billion. A closer look at the direct health care costs reveals that hospitalization is still the major cost driver both for CHD and stroke. However, social service costs are also very important for stroke, whereas indirect costs are of less importance because of the age distribution.

Very few studies report separate estimates for men and women. However, a study from Germany reports total direct cost for CVD in 2002 of 35.4 billion €, of which 16.1 billion for men and 19.2 billion for women.<sup>79</sup> Costs are higher for men in the age group under 65 years, but the reverse is true for the age group over 65. Men have higher costs related to CHD but women have higher costs related to hypertension, heart failure, and cerebrovascular disease.

Another way of looking at costs of CVD is to estimate the extra life-time costs on the basis of the incidence. Sasser *et al.*<sup>80</sup> studied life-time medical costs for women due to CVD, diabetes, and urinary incontinence. Total life-time cost of CVD was calculated to be 423 000 US\$. This cost for a woman with CVD is 3.4 times higher than that for a woman without heart disease and 2.5 times higher than that for a woman with diabetes.

It has been reported that in Sweden, the life-time cost of a stroke is between 40 000 and 60 000 € dependent on age. Life-time costs are significantly higher for women than men in the age group over 65, when the majority of strokes occur. This is consistent with the results from Germany based on prevalence.<sup>79</sup>

### Health care interventions and cost-effectiveness

Over the last decades, a number of new interventions and technologies have been introduced for the prevention, treatment, and rehabilitation of CVD. They include the development of new drugs for hypertension and dyslipidaemia, new techniques for surgical and endovascular coronary revascularization, more sophisticated pacemakers, and implantable defibrillators, as well as the introduction of new health care modalities such as stroke units and cardiac rehabilitation programs, including life style interventions. Owing to the higher costs of these interventions, there has been also an increasing interest to provide evidence that new technologies not only are safe and effective but also cost-effective.<sup>81</sup> These studies only seldom evaluated separately men and women, as clinical trials often do not have enough power for subgroup analysis by gender. Accordingly, at the present time, to address the issue of cost-effectiveness in women, one should rely on modelling studies.

As an example, the cost-effectiveness of lipid lowering agents in secondary prevention has been questioned for women.<sup>82</sup> However, the cost-effectiveness analysis performed by gender in relation to baseline levels of total cholesterol shows that this intervention is very cost-effective, also for young women with low cholesterol levels. In fact, if indirect costs are included, this intervention is even cost-saving in younger women.

Another example comes from the analysis of the CURE trial, a study on secondary prevention after ACS.<sup>83</sup> It has been shown that adding clopidogrel to aspirin at the time and after an ACS is a cost-effective intervention for both men and women, with or without percutaneous revascularization.

Another issue is the relation between cost-effectiveness and guidelines for clinical practice. According to guidelines, on the basis of risk stratification of the SCORE charts, interventions should be based on absolute risk. Women carry a lower absolute risk than men, but when an event occurs, the consequences in terms of costs and loss of quality-adjusted life expectancy are greater than in males. Thus, in order to avoid under-treatment of women, intervention thresholds should be adjusted according to gender.

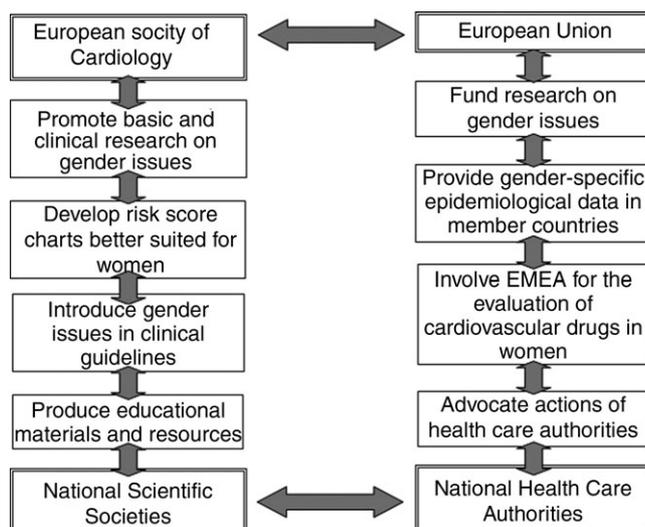
*There is evidence that CVD is underestimated as a health problem for women. Accordingly, systematic studies on the costs of CVD and the cost-effectiveness of interventions from a gender perspective should help in the allocation of health care resources even in a setting of resource constraints.*

## Conclusions

The Policy Conference of the European Society of Cardiology has provided the opportunity to review and comment on the current status of knowledge on CVDs in women and to prioritize the actions needed to advance this area of knowledge in Cardiology. In the preparation of this document, we intend to provide the medical community and the stakeholders of this field with an overview of the more critical aspects that have emerged during the discussion. We also propose some immediate actions that should be undertaken with the hope that synergic activities will be implemented at European level with the support of national health care authorities (Figure 4).

## Priorities and recommendations for research and clinical trials

- (i) The lack of conclusive data on the magnitude of gender differences in response to cardiovascular therapy should stimulate basic and clinical research to advance the knowledge on gender-specific issues in cardiovascular pharmacology.



**Figure 4** Flowchart illustrating synergic activities that should be implemented at European level involving the European Society of Cardiology, the European Union, the National Scientific Societies and the National Health Care Authorities.

- (ii) Although non-pre-specified, *post hoc*, subgroup analysis by sex may help exploring the gender issues, targeted clinical trials are strongly needed and should be encouraged by National and European research funding agencies.

## Priorities and recommendations for education

- (i) Educational activities to increase awareness about morbidity and mortality related to CVDs in women should be implemented and targeted to different audiences including:
  - (a) Health care professionals
  - (b) Scientific Societies
  - (c) European institutions and national health care authorities
  - (d) Patients's Associations and Foundations
  - (e) General population

## Priorities and recommendations for the improvement of risk stratification, diagnosis and treatment of CVDs in women

- (i) Collect epidemiological data for CVDs and risk factors in women of different age groups in the European countries in order to improve the accuracy of risk charts to predict the risk of cardiac events in females.
- (ii) Tailor the risk assessment process to incorporate risk factors that are particularly important for women, i.e. diabetes and obesity.
- (iii) Extend risk assessment to older age groups in order to account for the delayed onset of CVDs in women.
- (iv) Encourage the assessment of the predictive value of diagnostic procedures by gender.
- (v) Promote the implementation of the recommendation of clinical guidelines with respect to the adoption of preventive measures and optimal medical therapy in women.
- (vi) Introduce gender issues in the clinical guidelines.
- (vii) Perform analysis by gender of ongoing surveys, databases and registries across Europe.
- (viii) Develop new surveys in the areas where data are lacking (i.e. stroke).

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**Conflict of interest:** none declared.

## Appendix. Participants

Participants in the ESC Policy Conference were (by role and alphabetic order):

**Speakers and Chairpersons:** Jean-Pierre Bassand, Raffaele Bugiardini, Peter Collins, Filippo Crea, Caroline Daly, Guy De Backer, Patricia Duquette, Kim M. Fox, Anselm K. Gitt, Ian Graham,

Christian W. Hamm, Bengt Jonsson, Peter Kearney, Susanne Logstrup, Attilio Maseri, Philip A. Poole-Wilson, Silvia G. Priori, Annika Rosengren, Susana Sans, Karin Schenck-Gustafsson, Marco Stramba-Badiale, Michal Tendera, Susanne Volqvartz, David Wood.

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