Gender-specific prescription for cardiovascular diseases?

Marco Stramba-Badiale¹ and Silvia G. Priori²,3*

¹Department of Cardiology, Istituto Auxologico Italiano IRCCS, Milan, Italy; ²Molecular Cardiology, IRCCS Fondazione Maugeri, University of Pavia, Via Ferrata 8, 27100 Pavia, Italy; and ³Department of Cardiology, University of Pavia, Pavia, Italy

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This editorial refers to 'Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases'¹ by N. Jochmann et al., on page 1585

The interest of the scientific and medical community on the impact of cardiovascular diseases in women has significantly grown in the last few years. Cardiovascular disease is indeed the leading cause of death among both women and men, even if this unequivocal epidemiological observation had not been taken into the right consideration in the past. Although cardiovascular diseases are equally important in men and women, gender differences in the clinical manifestation and progression of the disease have been demonstrated. The understanding of these differences is of crucial importance for the improvement of the clinical management of cardiovascular diseases and for the development of possible new gender-specific diagnostic and therapeutic options.

Women, for many years, have been underrepresented in randomized clinical trials and only recently there has been a significant increase in the number and proportion of women who participate in these studies. Accordingly, the possibility of different responses to pharmacological therapy in women and in men has recently emerged as part of the gender-related issues of cardiovascular disease. The review by Jochmann et al.¹ addresses the gender differences in pharmacokinetics, pharmacodynamics, and physiology which may contribute to a different response to cardiovascular drugs in women when compared with men. The authors analysed several clinical trials of cardiovascular drugs which involved a significant proportion of women as well as the studies which specifically addressed the issue of gender differences in pharmacokinetics and pharmacodynamics of agents utilized for prevention and treatment of cardiovascular disease.

It is interesting to note that of the 300 new drug applications received by the Food and Drug Administration (FDA) between 1995 and 2000, only 163 included an analysis according to gender. However, 11 of these drugs showed a difference in pharmacokinetics between men and women.²

The differences between women and men in the response to drugs are related to a lower body weight, smaller organ sizes, and a higher proportion of fat in women when compared with men. In addition, hormone levels and differences in metabolism may affect absorption and elimination of drugs in women.²

The cytochrome P450 (CYP) enzymes are responsible for the metabolism of most cardiovascular drugs, including many antiarrhythmics, and beta-blockers. Genetic polymorphisms in the expression of several CYP enzymes involved in drugs metabolism may influence the manifestation of adverse events and the efficacy of several agents. Gender differences in enzymes’ activity have been demonstrated for several CYP metabolized drugs, including diltiazem, nifedipine, and verapamil, with a significantly increased activity in women when compared with men. Gender differences in the elimination of drugs may also play a role, as the glomerular filtration rate is lower in women than in men, even after adjustment for body size.²

All these differences may account for gender effects on both adverse reactions and efficacy of cardiovascular drugs. In the DIG trial, it has been shown that women affected by heart failure who received digoxin had a higher mortality than those receiving placebo.³ This effect was not observed in men. Notably, only 2.3% of men compared with 3.4% of women had digoxin concentrations >2.0 ng/mL. The observation that the oral clearance of digoxin, a drug mostly eliminated by the kidney, is lower in women than in men may partially explain these different effects of digitalis on mortality.

Women have a greater risk of developing some specific adverse drug reactions than men. The prevalence of drug-induced torsades des points is higher in women than in men. A review of reported cases of cardiovascular drug-related torsades des points showed a female prevalence of 70%.⁴ Among patients who received dl-sotalol, torsades des points developed in 1.9% of males and in 4.1% of females, and proarrhythmia associated with the administration of erythromycin was also more common in women than in men, as shown by the Food and Drugs Administration database, where 67% of subjects who experienced life-threatening arrhythmias were females.⁵ Female gender is associated with a longer QT interval corrected for heart rate (QTc), an effect which is not present at birth and
becomes evident after puberty. A further QT interval prolongation at long cycle lengths and a more significant effect of QTc-prolonging drugs in women as compared to men have been demonstrated. Moreover, gender differences have been shown in the clinical manifestation and in the effect of QTc-prolonging drugs in women as compared to men. Studies. It is possible that gender differences at molecular level until very recently, as data were mainly based on studies conducted almost exclusively in men. This gap has been filled by the recently published Women’s Health Study, a large randomized, double-blind, placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among 39 876 healthy women. This study failed to show a benefit in the prevention of myocardial infarction. In addition, a random-effects meta-analysis that included data from the Women’s Health Study as well as data from five prior trials involving 55 580 participants with no history of heart disease also indicates that aspirin therapy was associated with a significant 1% reduction in the risk of stroke, with no reduction in the risk of myocardial infarction in women. These results are obviously in sharp departure from those obtained in male populations, which indicated that aspirin therapy is associated with a significant reduction of the risk of myocardial infarction. As women have a relatively greater incidence of strokes than of myocardial infarctions when compared with men, this observation is particularly relevant and may have important implications for the clinical practice. The reasons for these gender differences in the efficacy of aspirin for primary prevention remain to be elucidated and will require further studies. It is possible that gender differences at molecular and cellular levels may affect the development of cardiac and cerebrovascular diseases.

These observations underlie the importance of studying women as well as men in major cardiovascular clinical trials. Most of the progresses in this direction have occurred in the USA as a direct consequence of the commitment of funding agencies that have provided economical support to clinical trials only when a balanced gender presence was assured in the design of the trial. In Europe, there is no regulation of this type and therefore there is less sensitivity to the issue. Once again, Scientific Societies should play a major role in ensuring that gender-specific response to therapy is investigated in clinical trials.

The European Society of Cardiology (ESC) has recently developed the ’Women at Heart’ programme in order to organize initiatives targeted at promoting research and education in the field of cardiovascular diseases in women. The Policy Conference on Cardiovascular Diseases in Women held in Nice in June 2005 has brought together cardiologists from the ESC member countries with the objective to review current knowledge and to set the priorities for actions to be taken to fill knowledge gaps about cardiovascular diseases in women. Moreover, the strategies for changing the misperception of cardiovascular disease in women, improving risk stratification, diagnosis, and therapy from a gender perspective, and increasing women representation in clinical trials have been discussed.

Special focus on women and cardiovascular diseases will be given at the ESC Congress in Stockholm. These will in fact be a leading theme of the congress and scientific sessions dedicated to gender-specific issues will be identified by the ’pink heart’, symbol of the ‘Women at Heart’ ESC programme. Activities dedicated to women’s health and cardiovascular disease prevention have been also organized during the ESC public event ‘For your Heart’s Sake’, including specific information on risk factor reduction through lifestyle improvements during the Congress in Stockholm.

Moreover, the ESC has planned to perform an analysis of the Euro Heart Survey databases to obtain gender-specific data on heart failure, diabetes, angina, acute coronary syndromes, and atrial fibrillation. The Euro Heart Survey programme is aimed at monitoring clinical practice in Europe and to derive information on patients’ profile and clinical management in different cardiovascular diseases.

It is the hope of the ESC that the ‘Women at Heart’ programme would contribute to increase the awareness of the fact that cardiovascular disease is the primary cause of death in women and to improve the knowledge of risk factors, presentation, and treatment of cardiovascular diseases in women. For the next few years to come, the ESC has set an even more ambitious goal, and will try to promote a larger representation of women in clinical trials in order to provide missing data on gender differences in response to drug therapy.

References


