Gender differences in the outcome of noninvasive cardiovascular treatment

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Cardiovascular diseases are equally common in both sexes with differences in pathogenesis, clinical presentation and outcome. The incidence of cardiovascular diseases progressively increases in women after the menopause and their development is related to risk factors and their interaction with the female hormones. The prognosis after myocardial infarction is worse in women because of a more difficult diagnosis (atypical symptoms, unclear ECG abnormalities) and because of social and economic factors. The role of hormone replacement therapy in atherosclerosis prevention is not yet clear, and there are many doubts about its administration because of the increased risk of breast cancer and cardiovascular events.

Our best weapons against cardiovascular diseases are primary prevention and pharmacological therapy. The biological and pathophysiological mechanisms related to estrogen deficiency that may lead to the development of atherosclerosis are still unknown. Therefore, it would be useful to investigate the pathophysiology of atherosclerosis in women in order to improve primary prevention and the diagnostic and therapeutic strategies.

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Introduction

Epidemiological data[1,2] show that cardiovascular diseases are common both in men and women, who however present with many differences in pathogenesis, clinical presentation and outcome. The incidence of cardiovascular diseases progressively increases in men after 35 years of age, whereas in women after 55 years[1], that is a few years after the beginning of menopause. In particular, the onset and development of coronary heart disease (CHD) in women are closely related to the different role played by risk factors and to their interaction with ovarian hormones. The combination of various risk factors was most relevant in the Chicago Heart Association Detection Project in Industry[3] and in the Framingham Offspring Study[4]. The first study took into account smoking habit, hypertension, and hyperlipidemia in 8686 women and in 10 503 men (age range 40-64 years, mean follow-up 22 years). It has been found that the coronary mortality was higher among patients with multiple risk factors (two risk factors in 34% of women and in 38% of men and three risk factors in less than 7% of the total population) than in patients with a single risk factor (about 80%). The Framingham study evaluated hypercholesterolemia, lower levels of high-density lipoprotein (HDL) cholesterol, body mass index, systolic pressure, and triglyceride and glucose levels. About 17% of patients (age range 30-47 years, follow-up 16 years) had three of the six risk factors: 4% of previously asymptomatic women and 13% of men had new coronary events; these were associated with three or more risk factors in 48% of women and in 20% of men.

A recent study[5] showed that women with a low risk profile – non-smokers, blood pressure ≤ 120/80 mmHg, total cholesterol < 200 mg/dl, no diabetes or previous acute myocardial infarction (AMI), and a normal ECG – have an appreciably lower mortality.

In conclusion, these studies demonstrate that women without traditional risk factors have a lower probability of coronary events. Major benefits are achieved by aggressive preventive measures in women presenting with many risk factors or previous coronary events[6-8].

Gender differences in the treatment and prognosis of cardiovascular disease

Chest pain in women is atypical in a higher percentage than in men, and frequently it is not related with significant

CHD. Accordingly, coronary angiography is able to detect a significant coronary stenosis only in 72% of women with typical chest pain, vs 93% of men[9,10]. Therefore, because of the low specificity of symptoms and the difficulties in making a diagnosis, women are prescribed optimal medical therapy less frequently than men. Nonetheless, there are no significant gender differences in terms of treatment benefits[11-13].

As for acute coronary syndromes, an AMI as the first clinical sign of CHD occurs in about one third of women and in about 50% of men[1]. Women with unstable angina present less severe angiographic coronary injuries and a lower incidence of AMI or death at 30 days[14]. AMI is more often clinically silent or misdiagnosed than in men (women 34%, men 27%)[1,15].

Other gender differences can be observed in the clinical presentation of AMI: chest pain is a common symptom among men, whereas atypical symptoms such as dyspnea and/or nausea, and weakness are more common among women[16]. ECG abnormalities differ according to gender: ST-segment changes are less significant in men than in women[17]. Yet, it is not clear whether a worse prognosis after AMI in women with respect to men depends on[1,18-20] a more advanced age and/or a higher level of co-morbidity (hypertension, diabetes, left ventricular dysfunction, congestive heart failure) in the female gender[21]. However, several data show that the overall prognosis remains worse in women[20] even after risk factor adjustment. This may be due to a more difficult AMI diagnosis in women, because of atypical symptoms and/or the presence of unclear ECG abnormalities. For these reasons, women are often treated belatedly and, consequently, are often not eligible for thrombolysis. Finally, social and economic factors, such as the more advanced age of women with AMI, their lower income and the longer time gap between symptom onset and clinical evaluation, may have an important role[22]. Recent data from the National Registry of Myocardial Infarction-I[23] demonstrated a higher in-hospital mortality rate in women, possibly due to the delayed admission to the coronary care unit and to the lesser use of thrombolytic therapy, aspirin, heparin and beta-blockers. Women underwent additional procedures, such as angiography or angioplasty, less frequently than men. Finally, for similar treatment strategies the mortality rate was found to be substantially higher in the former.

The GUSTO IIb trial[14] reported no differences between the sexes regarding the clinical presentation and prognosis. It is important to stress that 45.9% of women vs 35.6% of men ($p < 0.001$) had unstable angina. Females had more risk factors and concomitant diseases. With regard to AMI, only 27.2% of women vs 37% of men presented ST-segment elevation at ECG, and the 30-day mortality was higher among women (6 vs 4% of men); nevertheless, the re-infarction rate was similar in both sexes (6.2 vs 5.6% of men, $p = 0.19$), with some differences justified by the variability in the baseline characteristics, such as a more advanced age and concomitant diseases. Hemorrhagic complications were more frequent in women.

Furthermore, the NRMI-2 trial[24] investigated the influence of the interaction between gender and age on the prognosis of AMI. Women were frequently older and presented more concomitant diseases than men. The early mortality after admission for AMI was 14% in females and 10% in males. The 30-day mortality was twice as high in women aged between 30 and 50 years than in men of the same age; it progressively decreased with aging and reached the parity after 75 years of age. Therefore, the prognosis in younger women is worse than in men; this observation undoubtedly changed the widespread opinion that the mortality after AMI is higher in women, because of their more advanced age.

The aforementioned studies all agree that there are many and important gender differences in the clinical presentation, prognosis and medical treatment of patients suffering from AMI[25]. Even in secondary prevention, treatments that are as effective in males as in females (aspirin, statins, anti-ischemic agents) are prescribed infrequently, and goals are hardly achieved (e.g. to reach optimal levels of low-density lipoprotein-LDL or HDL cholesterol)[12]; despite its effectiveness in both sexes[26], not even rehabilitative therapy is regularly prescribed.

Therefore, the higher mortality rate in women, after an acute coronary event, is due not only to their more advanced age, but, most of all, to differences in treatment.

Therefore, it is very important to look for gender differences in the clinical presentation of cardiovascular diseases, so that our knowledge, and consequently our therapeutic prescriptions, may be improved. Moreover, studying the cardiovascular risk profile in women may lead to the discovery of "specific risk factors" and then to the identification of "naturally protective factors" in the development of CHD.

Hormone replacement therapy

The aforesaid epidemiological data showed that cardiovascular diseases are more frequent in women after the menopause. For this reason, many authors tried to understand whether hormone replacement therapy (HRT) could have a role in preventing the development of atherosclerosis. Estrogens, in fact, have vasoactive properties, such as vasodilation as they increase the endothelial release of nitric oxide and act on the arterial smooth muscle cells in a manner similar to calcium channel blockers[27]. Moreover, these hormones promote an increase in HDL and LDL cholesterol receptors, and a decrease in LDL cholesterol. Besides, there is a relationship between their deficiency and the

development of hypertension. Therefore, menopause may cause a change in women's cardiovascular risk profile, which is largely influenced by estrogen deficiency.

Although several observational studies demonstrated the efficacy of HRT in decreasing the incidence of coronary events and the symptoms related to menopause[28,29], there are still many doubts about its administration, on account of the increased risk of ovarian, endometrial and breast cancer and of the risk of cardiovascular events.

The Women's Health Initiative (WHI) trial[30] was addressed to the evaluation of the risks and benefits of HRT (0.625 mg of estrogens + 2.5 mg of medroxyprogesterone acetate) in primary prevention (16 608 women, mean age 63.3 ± 7.1 years, mean follow-up 5.2 years). This study demonstrated an increased risk of breast cancer and cardiovascular events (AMI, stroke, pulmonary embolism, deep venous thrombosis) and a significant reduction in risk of colorectal cancer and, eventually, hip fracture (37 and 33%, respectively) among women on HRT. The adverse event rate starts to increase between the first and the second year of follow-up, whereas the breast cancer rate increases after the third year. The total mortality rates are indistinguishable between HRT and placebo.

These are certainly noteworthy results, but WHI has some limitations: in fact, it only takes into account one treatment schedule, thus not allowing us to distinguish the effect of a given treatment alone (estrogen or progestin) and, conversely, to verify the effect of other therapeutic schedules, in terms of the dose and route of administration. In any case, a parallel trial of estrogen alone in women who have had a hysterectomy is in preparation (planned end March 2005, average follow-up 8.5 years).

Let us consider the real incidence of adverse effects: among 10 000 women taking the drug for 1 year, there will be 7 more patients who develop CHD events, 8 more patients who develop an invasive breast cancer, 8 more patients who develop stroke, and 8 more patients with pulmonary embolism. On the other hand, there will be 6 patients less with colorectal cancer and 5 patients less with a hip fracture. All the same, counting all events over the 5.2 years of the trial, the excess number of events was 100 per 10 000 (i.e. 1%). This is but a small risk, and yet it demonstrates that the risks related to the drug sum up over time.

HRT was evaluated to verify its possible benefits in secondary prevention as well. The HERS trial[31], the first randomized, blinded, placebo-controlled one, was designed with the aim of verifying the hypothesis that HRT reduces the coronary event incidence in women with documented CHD (2763 women, aged < 80 years and followed up over 4 years).

Among women on HRT, there was a reduction in LDL cholesterol and an increase in HDL cholesterol, but not a significant difference between groups in the total mortality and in the incidence of coronary events (AMI, angina, cardiovascular death and myocardial revascularization procedures). During the first year of follow-up, cardiovascular events increased among women who were taking the drug, whereas they began to decrease after the fourth-fifth year. Moreover, there was a significant increase of thromboembolic events and biliary tract surgery. However, the HERS trial has some limitations too:

- the short-term follow-up does not allow one to assess the possible long-term favorable effects;
- some of the negative effects may be due to progestin hormone;
- the advanced age of the patients (mean age 66.7 years).

The long-term follow-up (6.8 years) results of the recently published HERS II trial[32] demonstrate that HRT does not reduce the long-term risk of cardiovascular events in women with CHD.

Conclusions

The longer life expectancy in women keeps level with an increase in the incidence of CHD; consequently, it is time for an adequate primary prevention.

Our best strategies against CHD are: a reduction in risk factors, lifestyle interventions (smoking avoidance, proper nutrition and regular exercise), and pharmacological therapy (lipid-lowering, blood pressure and glycemia control).

The prognosis after AMI, and particularly after ST-elevation AMI, seems to be worse in females than in males, even though this difference is not completely explained by the more advanced age of women, thrombolytic therapy, concomitant diseases, and by the severity of coronary injuries. It could probably be explained by a higher risk factor rate among females, recurrent ischemia and under-usage of therapies, which have the same efficacy in both sexes. A recent American Heart Association statement[33] recommends the control of risk factors to all women, and a specific therapy with antiplatelet agents or anticoagulants (when indicated), beta-blockers, and ACE-inhibitors to those with existing CHD, according to their clinical conditions.

The real benefits of HRT for the prevention of CHD in postmenopausal women are not yet clear. Moreover, in spite of the valid basal theories, the biologic and pathophysiological mechanisms related to estrogen deficiency that can lead to changes in the lipid profile and then to CHD, are still unknown.

Therefore, nowadays it is useful practice to investigate the pathophysiological mechanisms that lead to the development of atherosclerosis in women, in order to achieve an effective primary prevention, improve diagnostic strategies, provide more evidence for the utilization of HRT in the prevention of CHD.

References

1. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986; 111: 383-90.
2. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring Trends and Determinants in Cardiovascular Disease. Lancet 1999; 353: 1547-57.
3. Lowe LP, Greenland P, Ruth RJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Arch Intern Med 1998; 158: 2007-14.
4. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. Arch Intern Med 1999; 159: 1104-9.
5. Stamler J, Stamler R, Neaton JD, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adults and middle-aged men and women. JAMA 1999; 282: 2012-8.
6. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary versus secondary prevention. Arch Intern Med 1998; 158: 655-62.
7. Perlman JA, Wolf PH, Ray R, Lieberknecht G. Cardiovascular risk factors, premature heart disease, and all-cause mortality in a cohort of northern California women. Am J Obstet Gynecol 1988; 158 (Part 2): 1568-74.
8. Newnham HH, Silberberg J. Coronary heart disease. Women's hearts are hard to break. Lancet 1997; 349 (Suppl 1): SI3-SI6.
9. National Center for Health Statistics. Health, United States, 1990. Hyattsville, MD: Public Health Service, 1991.
10. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979; 301: 230-5.
11. Goldberg RJ, Larson M, Levy D. Factors associated with survival to 75 years of age in middle aged men and women. The Framingham Study. Arch Intern Med 1996; 156: 505-9.
12. Majumdar SR, Gurwitz JH, Soumerai SB. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. J Gen Intern Med 1999; 14: 711-7.
13. Collins LJ, Douglas PS. Acute coronary syndromes. In: Charney P, ed. Coronary artery disease in women: prevention, diagnosis and management. Philadelphia, PA: American College of Physicians, 1999: 407-13.
14. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 1999; 341: 226-32.
15. Johansson S, Bergstrand R, Schlossman D, Selin K, Vedin A, Wilhelmsson C. Sex differences in cardioangiographic findings after myocardial infarction. Eur Heart J 1984; 5: 374-81.
16. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction. Results from the Myocardial Infarction Triage and Intervention Registry. Arch Intern Med 1992; 152: 972-6.
17. Dellborg M, Herlitz J, Emanuelsson H, Swedberg K. ECG changes during myocardial ischemia. Differences between men and women. J Electrocardiol 1994; 27 (Suppl): 42-5.
18. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1524 women after myocardial infarction. Comparison with 4315 men. Circulation 1991; 83: 484-91.
19. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Engl J Med 2000; 343: 8-15.
20. Tofler GH, Stone PH, Muller JE, et al. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol 1987; 9: 473-82.
21. Fiebach NH, Viscoli CM, Horwitz RI. Differences between women and men in survival after myocardial infarction. Biology or methodology? JAMA 1990; 263: 1092-6.
22. Klein W. Cardiovascular disease at the turn of the millennium: focus in Europe. Eur Heart J 2001; 3 (Suppl M): M2-M6.
23. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998; 158: 981-8.
24. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999; 341: 217-25.
25. Woodfield SL, Lundergan CF, Reiner SJ, et al. Gender and acute myocardial infarction: is there a different response to thrombolysis? J Am Coll Cardiol 1997; 29: 35-42.
26. Fair JM, Berra K, King AC. Exercise as primary and secondary prevention. In: Charney P, ed. Coronary artery disease in women: prevention, diagnosis and management. Philadelphia, PA: American College of Physicians, 1999: 209-35.
27. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med 1999; 340: 1801-11.
28. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997; 336: 1769-75.
29. Session DR, Kelly AC, Jewelewicz R. Current concepts in estrogen replacement therapy in the menopause. Fertil Steril 1993; 2: 277-84.
30. Rossouw JE, Anderson GL, Prentice RL, et al, for the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-33.
31. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280: 605-13.
32. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart an Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288: 49-57.
33. Mosca L, Collins P, Herrington DM, et al. Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 2001; 104: 499-503.