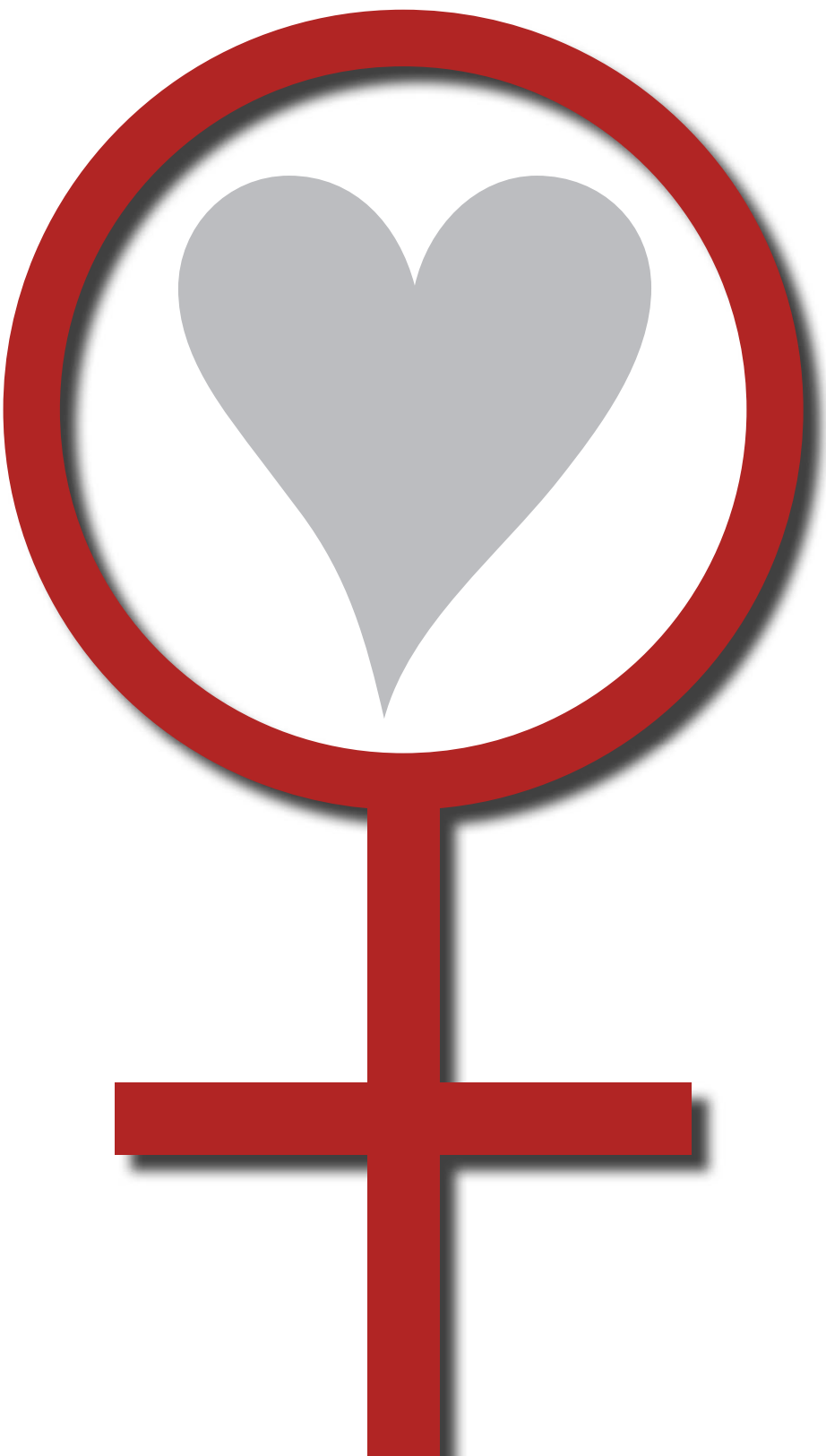
Red Alert for Women's Hearts

Women and Cardiovascular Research in Europe

November 2009



EUROPEAN HEART NETWORK

EUROPEAN SOCIETY OF CARDIOLOGY®

Red Alert on Women's Hearts

Women and Cardiovascular Research in Europe

November 2009

European Heart Health Strategy
EuroHeart Project, Work Package 6
Women and Cardiovascular Diseases

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Table of Contents

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Summary

Cardiovascular diseases represent the major cause of mortality in women and in men. The results of large randomized clinical trials allowed the introduction of preventive measures and effective treatments with a significant improvement of survival and reduction of disability. However, sex and gender differences in the clinical presentation of cardiovascular diseases have been demonstrated and some therapeutic options may not be equally effective and safe in men and women. Under-representation of women in cardiovascular research has been clearly demonstrated in the past and, recently, efforts to enrol a larger number of women in clinical trials have been made.

One of the objectives of Work Package 6 of the EuroHeart project, conducted jointly by the European Heart Network and the European Society of Cardiology, was to assess the representation of women in cardiovascular research in Europe. A search was conducted in order to identify publications (European or international with European representation) of randomized clinical trials which enrolled women and men or women only.

The 62 randomized clinical trials published since 2006 and analyzed here, enrolled overall 380,891 participants and 127,716 were women (33.5%) (See table 1 on page 31 for a summary). Mean age of participants was 66.3 years and mean follow-up 2.7 years. The percentage of women enrolled in each trial ranges from 15% to 60%, but only 31/62 trials (50%) reported the analysis of the results by gender. The representation of women in the clinical trials is not homogeneous. Trials performed on blood pressure lowering therapies, diabetes, atrial fibrillation and stroke enrolled approximately 40% of women, while trials performed on cholesterol-lowering therapy and on management and treatment of ischemic heart disease and heart failure enrolled about 30% of females. Most of the clinical trials and meta-analyses on cardiovascular diseases did not report a significantly lower effi cacy of interventions in the outcomes in women when compared with men. For some therapies there is even a suggestion for greater effi cacy in women than in men, as in the case of cardiac resynchronization therapy in heart failure or thrombolysis after ischemic stroke. Women may have more frequently adverse effects, such as for newer glucose-lowering agents, or in the treatment of acute coronary syndromes, where they appear to be more prone to bleedings. Some trials provided conflicting results in women, for example in the assessment of the effi cacy of early invasive strategies in acute coronary syndromes.

Despite an increase in the number and proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischemic heart disease and heart failure, which may have affected the reliability of subgroup analysis.

Although gender issues are addressed, Scientific Guidelines do not generally provide specific recommendations for prevention or treatment in women. Thus, despite an increase in the number and proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischemic heart disease and heart failure, which may have affected the reliability of subgroup analysis. Furthermore, approximately 50% of the trials did not report an analysis of the results by gender. Clinical trials enrolling only female patients or clinical trials enrolling a significant proportion of women to allow for prespecified gender analysis should be conducted. Initiatives which contribute to increase the awareness in Europe that cardiovascular diseases are the major cause of death in women and to improve the knowledge of risk factors, presentation and treatment of cardiovascular diseases in women should be encouraged. Scientific societies, patients' associations and foundations should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on gender issues in cardiovascular medicine and a larger representation of women in clinical trials.

Introduction

Despite a significant decline in the incidence of cardiovascular diseases in the last 50 years, ischemic heart disease and stroke still represent the major cause of mortality, morbidity and disability in women as well as in men (1). The identification of risk factors for cardiovascular diseases in large epidemiological studies allowed the performance of randomized clinical trials to test the effi cacy and safety of preventive interventions. Furthermore, significant improvement of survival and reduction of disability has been made possible by clinical research on interventions in the acute phase of cardiovascular events and on the effi cacy of long-term therapies for secondary prevention.

However, gender differences in the clinical presentation of cardiovascular diseases have been demonstrated (2) and some therapeutic options may not be equally effective and safe in men and women (3). Accordingly, it is crucial that preventive and therapeutic interventions are tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk. Under-representation of women in cardiovascular research has been clearly demonstrated in the past. More recently, special attention has been paid to the issue of cardiovascular diseases in women and there is a growing interest for gender-specific cardiovascular medicine. Scientific societies, patients associations and heart foundations undertook several initiatives to increase the awareness of cardiovascular diseases in women and the representation of female gender in clinical research. Regulatory agencies in the USA but also in Europe have tried to encourage the inclusion of a higher proportion of women in clinical trials and some studies have been performed in populations of women only (4).

The European Heart Health Strategy (EuroHeart) project is a joint initiative of the European Society of Cardiology (ESC) and the European Heart Network (EHN), co-funded by the European Commission and launched in April 2007. One of the objectives of this project is to improve the awareness, diagnosis and treatment of cardiovascular diseases in women across Europe. One specific aim was to analyze campaigns targeting women to increase their awareness of cardiovascular diseases as well as educational programmes for health professionals. Another objective was to address the issue of women representation in cardiovascular clinical research by collecting information on clinical trials and registries in Europe. Furthermore, possible gender differences in the primary outcomes of these trials and in the current clinical practice together with the presence of gender issues in Scientific Guidelines of European scientific societies have been assessed. This document summarizes the results of the analysis by critically reviewing the most significant findings. The analysis of the awareness campaigns and educational programmes is described elsewhere.

Background

Gender, epidemiology of cardiovascular diseases, and inequalities in life expectancy among European countries

Cardiovascular diseases are the leading cause of death in men and women, as indicated by data released in 2008 by the World Health Organization, accounting for 43% of deaths in men and 54% in women in Europe (1). Specifically, coronary heart disease represents 21% of deaths in men and 22% in women, whereas stroke is a more frequent cause of death in women than in men (17% and 11%, respectively), as well as the other cardiovascular diseases (15% in women and 11% in men). Thus, stroke represents the third cause of death in men and the second in women.

In younger age groups the prevalence of cardiovascular diseases is lower in women when compared to men, and the reverse is true at older ages. The prevalence of stroke is slightly higher in men than in women, irrespective of age.

The prevalence and incidence of cardiovascular diseases among both men and women increase with age (2). However, in younger age groups the prevalence of cardiovascular diseases is lower in women when compared to men, and the reverse is true at older ages. The prevalence of stroke is slightly higher in men than in women, irrespective of age.

There has been an age-adjusted decline in mortality for cardiovascular diseases in the last 50 years in Western countries, but this decline was less pronounced in women.

Although life expectancy is increasing in Europe, significant inequalities have been demonstrated across the European countries (1). In Eastern Europe life expectancy is lower than in Western Europe with relevant gender differences. More specifically, in 2005 men of Eastern Europe showed an excess mortality of 13.3 years compared to men in Western Europe, mostly in the group below the age of 60, while the 7.9 years of excess mortality in women occurred at older ages. In fact, of the whole difference in life expectancy in men, approximately 65% was due to excess mortality in the 15–59-year age group, while in women the difference in life expectancy was largely the result of higher mortality in those over the age of 60 (contributing to 50%). The single most important contributor to excess mortality in Eastern Europe is cardiovascular disease. However, while among males less than 50% of the excess mortality was due to cardiovascular diseases, in females the contribution of cardiovascular diseases was approximately 80%

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Life expectancy might not fully reflect the actual health condition of the population. When life expectancy without activity limitation is considered, similar inequalities between European countries have been found (5). Healthy life years at age 50 by sex and country have been calculated for 25 countries in the European Union (before the enlargements to the last 2 new members). In 2005, an average 50-year-old man could expect to live until 67.3 years free of activity limitation, and a woman until 68.1 years. Of note, healthy life years at age 50 for both men and women varied between countries (from 9.1 years in Estonia to 23.6 years in Denmark for men; from 10.4 years in Estonia to 24.1 years in Denmark for women). Thus, citizens of the 15 European countries which formed the EU before the recent enlargements have both longer and healthier lives than do most of those of the 10 new European Union countries. These findings suggest

that, without major improvements in population health, life expectancy without activity limitation will remain lower in a significant proportion of the 25 European Union countries.

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Cardiovascular diseases in women: the need for action

In the last 20 years, several initiatives have been undertaken in order to increase the awareness and the management of cardiovascular diseases in women in different countries. One example is the "Go Red for Women" campaign conducted in the USA with the goal of reducing the impact of cardiovascular risk factors among women and increasing the knowledge of cardiovascular diseases among health professionals but also in the general population.

In 2005 the European Society of Cardiology launched the "Women at Heart" programme in order to organize initiatives targeted at promoting research and education in the field of cardiovascular diseases in women. Among these initiatives an analysis of the European Society of Cardiology Euro Heart Survey - a programme aimed at monitoring clinical practice in Europe - has been performed in order to assess possible differences between women and men in the management and treatment of cardiovascular diseases.

The European Society of Cardiology promoted also a Policy Conference, held in Nice in June 2005, with the objective of summarizing the state of the art in Europe, identifying the scientific gaps in research on cardiovascular diseases in women and delineating the strategies for changing the misperception of cardiovascular diseases in women, improving risk stratification, diagnosis and therapy from a gender perspective and increasing women representation in clinical trials. The Statement from the Policy Conference which summarized the main topics of the discussion and provided recommendations to diminish the impact of cardiovascular diseases in women has been published in the European Heart Journal and translated in different languages (2).

Under-representation of women in clinical trials

It has been suggested that gender differences in the response to cardiovascular therapy may be identified (3) and that understanding these differences may improve the clinical management of cardiovascular diseases and, in the future, develop possible gender-specific diagnostic and therapeutic strategies. However, women have been under-represented in randomized clinical trials and only recently the percentage of women enrolled has increased. As a consequence, safety and effi cacy of several drugs have been evaluated predominantly in male populations.

In a study funded by the NHLBI which investigated the enrolment of women in mixed-gender cardiovascular clinical trials between 1965 and 1998, the overall proportion of women enrolled was 38% (6). An updated analysis of the enrolment of women in mixed-gender NHLBI-sponsored randomized controlled trials with primary outcomes of stroke, myocardial infarction, or death published between 1997 and 2006 showed that the proportion of women was 27% and only 13 of 19 studies included in this analysis reported gender-based outcomes in their primary report (7).

In the cardiovascular clinical trials performed almost exclusively in European countries in the same period, the proportion of women enrolled varied between 16 and 25%, although the female prevalence of the clinical condition under study in the general population was similar to that of men.

In 2005, the European Medicines Agency (EMEA) released a document on gender considerations in the conduct of clinical trials, emphasizing the importance of a fair representation of women. Furthermore, the Policy Conference on Cardiovascular Diseases in Women (2) noted that there was a lack of conclusive data on the magnitude of gender differences in the response to cardiovascular therapies and an important recommendation was to stimulate basic and clinical research to advance the knowledge on this topic. Although non prespecified, 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, targeted clinical trials are needed. As a consequence, it was 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 prespecified gender analysis should be conducted (2).

The Policy Conference also recommended that synergic activities should be undertaken at European level with the support of national scientific societies, European institutions, national health care authorities, patients' associations and foundations. An important step was the Conference jointly organized by the European Heart Network and the European Society of Cardiology in March 2006 under the auspices of the Austrian Council Presidency, where the scientific community discussed the issues of cardiovascular diseases in women with representatives of the European Parliament, Ministries of Health of different European countries and representatives of heart foundations. During this Conference recommendations for action of the European Union to ensure that cardiovascular health for women is properly considered in all relevant European Union policies were adopted. The Conference recommended that gender-specific aspects should be promoted by the European Union and that dedicated research funding should be made available to advance gender-specific medicine.

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Women and research on cardiovascular diseases: the European Heart Health Strategy (EuroHeart) project

In 2006 the European Heart Network and the European Society of Cardiology jointly applied for a grant in the framework of the Programme of Community Action in the field of Public Health of the European Commission. The European Heart Health Strategy (EuroHeart) project was accepted for co-funding from the EU and started in April 2007. The general objective of the EuroHeart project was to address the significant burden of cardiovascular diseases in Europe and to determine specific areas of intervention to prevent avoidable deaths and disability. Specifically, the objectives were to strengthen cross-sector cooperation (Work Package (WP) 4), obtain comprehensive comparable information on policies and actions on cardiovascular health promotion and cardiovascular disease prevention (WP 5), improve the awareness, diagnosis and treatment of cardiovascular diseases in women across Europe (WP 6), improve prevention practices at primary care level (WP 7) and implement

and adapt European guidelines on CVD prevention to national situations (WP 8). In Work Package 6, one of the specific aims of the EuroHeart project was to collect information on clinical research and to identify the gaps in knowledge of cardiovascular diseases in women in Europe.

In order to assess the current representation of women in cardiovascular research, electronic literature search of Pub Med and International Controlled Trials website has been performed. The time period covered was from 2006 (to follow up from ESC 2006 conference on women and cardiovascular diseases) to June 2009. Four different types of publications (European or international with European representation) have been analysed: observational/epidemiological studies; randomized clinical trials, including meta-analyses, which enrolled women and men or women only; European registries, i.e. the Euro Heart Survey, on the status of clinical practice; Guidelines and Statements of European Scientific Societies.

The analysis focused on the number and percentage of women enrolled in the studies, age of participants, time of follow-up, availability of the analysis of outcomes by gender, identification of gender differences in risk, outcome or clinical practice, and inclusion of gender issues in European scientific guidelines.

Outcome of the research

Age, menopause and the cardiovascular risk in women

Age is an important risk factor for coronary heart disease and stroke in both genders, but women usually develop cardiovascular diseases 10 years later in life than men (2). The risk for cardiovascular diseases increases after menopause (8) partly because of ovarian hormone deficiency that favours hypertension, diabetes, hyperlipidemia, central obesity and the metabolic syndrome (2.7-9). Body weight may increase during the first year since menopause and body fat distribution changes from a gynoid (mainly to the hips and thighs) to an android pattern (mainly abdominal) (10). Central obesity increases the risk of cardiovascular events (2,11) and it is associated with other risk factors or co-morbidities. In fact, the metabolic syndrome, defined by the presence of three or more risk factors which include central obesity, is more prevalent in women than in men with coronary heart disease (12).

Changes in body weight together with the activation of the renin-angiotensin-aldosterone system, associated with postmenopausal estrogens deficiency may increase arterial blood pressure. Hypertension is more prevalent in men until 45 years but after that age the reverse is true (13), and in postmenopausal women systolic and diastolic blood pressure are higher than in premenopausal women (14). Moreover, plasma cholesterol reaches the highest values between 55 and 65 years of age in women (about 10 years later than in men) (11) and menopause is associated with an increase in total and LDL cholesterol and a decline in HDL levels. Besides the metabolic effects, menopause may also contribute to the development of atherosclerosis by inducing the endothelial dysfunction (15).

Since ovarian hormone deficiency is associated with an increased risk of cardiovascular diseases, it was hypothesized that the administration of estrogens in peri- and postmenopausal women would have exerted a cardiovascular protective effect. A meta-analysis of observational studies published in 1991 (16) showed a significant reduction in the relative risk for coronary heart disease associated with hormone replacement therapy (HRT). On this basis the Guidelines of scientific societies recommended that HRT should have been considered in all postmenopausal women to prevent coronary heart disease (17) and prescriptions of HRT rose in the 1990s. However, due to the lack of randomization, observational studies have limitations. In fact, several large controlled randomized trials subsequently performed did not confirm the reduced risk of cardiovascular diseases associated with HRT. A recent meta-analysis of 31 randomized clinical trials on 44,113 patients (18) has indeed shown that HRT is associated with an increased risk of stroke (odds ratio, OR, 1.32, 95% confidence intervals, CI, 1.14–1.53) and venous thromboembolism (OR 2.05, 95% CI 1.44–2.92), with no effect on coronary heart disease (OR 1.02, 95% CI 0.90–1.11), thus confirming a previous meta-analysis (19) (see appendix 1*). Stroke severity was also increased with HRT (OR 1.31, 95% CI 1.12–1.54). On the basis of the results of the randomized clinical trials the Guidelines have been changed and they do not recommend HRT for the prevention of cardiovascular diseases in postmenopausal women (20-22) and prescriptions of HRT significantly declined.

Of note, the randomized clinical trials on HRT have been performed with mainly one form of hormone therapy such as combined continuous equine estrogens and medroxyprogesterone acetate or continuous equine estrogen alone (23). However, the physiological and cardiovascular effects of ovarian hormones may change with different type, dose, duration, and mode of administration, as suggested by the recent findings that transdermal estrogens, at variance with oral preparations, do not seem to be associated with increased risk of venous thrombosis (24) and that oral, but not transdermal, preparations containing estradiol markedly increase C-reactive protein (24). In the ESTHER study (25), a multicenter case–control study among postmenopausal women aged 45 to 70, venous thromboembolism occurred more frequently in current users of oral estrogens than in non-users and in transdermal estrogens users.

* All appendices referred to in this report are available on-line on http://www.ehnheart.org/content/ItemPublication.asp?docid=7441&level0=1456&level1=2096&level2=2100

Although obtained in a non-randomized clinical trial, these results might suggest a safer profile of transdermal as compared to oral administration of sex hormones.

The lack of beneficial cardiovascular effects observed in the randomized trials may be partly due to the age of the population and the time of beginning of therapy since menopause. In fact, an increased risk of cardiovascular diseases was found in the oldest women and in those who started HRT late after menopause began (23), although a recent anlysis of the WHI trial showed that the risk may be present even soon after menopause (26). As randomized trials have shown a pattern of early harm followed by later benefit, it is possible that transient adverse effects on thrombogenesis occur in the first year after the beginning of therapy, whereas beneficial effects on cardiovascular risk factors may develop in the subsequent years (27). Further studies are necessary to assess the mechanisms underlying the detrimental or protective effects of HRT and to evaluate benefits and risks of different mode of administration, dosages and duration of HRT.

Different therapeutic approaches from HRT have been utilized in postmenopausal women. Non-hormonal interventions have not been proven to be equally effective in relieving symptoms of menopause (28). In the Raloxifene Use for The Heart (RUTH) trial (29) which enrolled 10,101 postmenopausal women (mean age, 67.5 years) with coronary heart disease or multiple risk factors for coronary heart disease, raloxifene, a nonsteroidal selective estrogen-receptor modulator that binds to the estrogens receptor, had no significant effect on the risk of coronary events (hazard ratio 0.95; 95% CI 0.84-1.07), and it reduced the risk of invasive breast cancer (hazard ratio 0.56; 95% CI 0.38-0.83). There was no significant difference in the rates of death from any cause or total stroke, but raloxifene was associated with an increased risk of fatal stroke (hazard ratio 1.49; 95% CI 1.00-2.24) and venous thromboembolism (hazard ratio 1.44; 95% CI 1.06-1.95). Raloxifene reduced the risk of clinical vertebral fractures (hazard ratio 0.65; 95% CI 0.47-0.89). Of note, the effect of raloxifene on the incidence of coronary events differed significantly by age. A post-hoc analysis showed that the incidence of coronary events in women <60 years of age was significantly lower in those assigned raloxifene compared with placebo while no difference was found between treatment groups in the incidence of coronary events in women >60 and <70 or >70 years of age (30).

Clear evidence on the safest hormone regimen is still lacking and there is a consensus that HRT should be prescribed for the reduction of menopausal symptoms only in younger postmenopausal women at low risk of cardiovascular diseases.

In the LIFT trial (30), a randomized study in 4,538 women with osteoporosis, aged between 60 and 85 years, tibolone, another compound which has estrogenic, progestogenic, and androgenic effects, decreased the risk of vertebral fracture (hazard ratio 0.55; 95% CI 0.41- 0.74), of nonvertebral fracture (hazard ratio 0.74; 95% CI 0.58 - 0.93), invasive breast cancer (hazard ratio 0.32; 95% CI 0.13 - 0.80) and colon cancer (hazard ratio 0.31; 95% CI 0.10 - 0.96). However, the tibolone group had an increased risk of stroke (hazard ratio 2.19; 95% CI 1.14 - 4.23), for which the study was stopped in February 2006. There were no significant differences in the risk of either coronary heart disease or venous thromboembolism between the two groups. These effects should be taken into consideration when considering the use of raloxifene or tibolone in postmenopausal women.

Thus, clear evidence on the safest hormone regimen is still lacking and there is a consensus that HRT should be prescribed for the reduction of menopausal symptoms only in younger postmenopausal women at low risk of cardiovascular diseases (15). The benefit of HRT in relieving menopausal symptoms and reducing the occurrence of hip fractures should always be weighted against the possible increased risk of cardiovascular diseases and breast cancer. As the identification of the presence of cardiovascular

risk factors for their control in the peri- and postmenopausal women is of crucial importance, a Task Force jointly promoted by the European Society of Cardiology and the International Menopause Society published a document which recommends the involvement of gynaecologists, who are the only physicians frequently seen by women in the absence of symptoms, for the prevention of cardiovascular diseases (32).

Cardiovascular risk assessment and management in women

The identification and control of cardiovascular risk factors represent the basis for the development of a preventive strategy. Unfortunately, women are less likely than men to identify their risk factors and to participate in screening programmes.

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Strategies for the control of risk factors have been outlined in the Fourth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (33). More emphasis on cardiovascular risk in women has been given in a separate session on gender issues in this updated version and the recommendations of the Policy Conference on Cardiovascular Diseases in Women have been acknowledged. The Guidelines stressed again the need to prevent all atherosclerotic cardiovascular diseases rather than just coronary heart disease, in the use of the cardiovascular risk prediction system (SCORE) (34). The SCORE charts provide means of determining the risk of dying from cardiovascular diseases in 10 years. The SCORE system is derived from data from 12 European Cohort studies that involved 205,178 individuals (93,298 women) and considers systolic blood pressure and serum cholesterol in relation to age and smoking in establishing absolute risk in either high- or low-risk European countries. As women experience cardiovascular events later in life, in particular fatal cardiovascular events as measured by SCORE, the absolute estimated rate of risk for a perimenopausal or an early postmenopausal woman may be low when compared with men, and large increases in relative risk may not be taken into account. To avoid such problems, the SCORE system may be used to estimate the risk projected to age 60 in patients with an unhealthy risk profile but with a low absolute level of risk. Also, the SCORE system may underestimate the risk in obese patients with low HDL, increased triglycerides or impaired glucose tolerance, all features of the metabolic syndrome which is a major component of cardiovascular risk in postmenopausal women, and does not take into account diabetes, which is relatively more important as a risk factor for cardiovascular diseases in women than in men.

On the basis of this observation, the Statement of the Policy Conference on cardiovascular diseases in women (2) recommends that both the absolute risk and relative risk should be estimated, since 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 account. Risk should be extrapolated to a higher age in women (70 years instead of 60 years).

Risk factors that are particularly important for women, i.e. diabetes and obesity, should be taken into account. Risk should be extrapolated to a higher age in women (70 years instead of 60 years).

In order to improve cardiovascular risk stratification in women some recent studies assessed new score

systems and novel markers. A study performed in the United States in approximately 25,000 healthy women age 45 and older, followed up for a median of 10.2 years tested a new risk algorithm, named Reynolds Risk Score (35). Two new variables, such as parental family history of premature coronary heart disease and high-sensitivity C-reactive protein (hsCRP), were added to the variables in the ATP-III risk score. At variance with the European SCORE system and similarly to the Framingham score, the outcome was not cardiovascular death but cardiovascular events, although stroke has been added to coronary heart disease. With this score system women were classified into higher- or lower-risk categories with improved accuracy compared with the currently used risk prediction model in the United States.

In the Nurses' Health Study which enrolled 121,700 women, plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker utilized for risk stratification in heart failure patients, have been found to predict risk of sudden cardiac death, after adjustment for coronary heart disease risk factors and other biomarkers (36).

Other markers, as plasma homocysteine, have been found to be associated with a higher risk of ischemic heart disease and stroke, but its reduction induced by the administration of folic acid, vitamin B12 or vitamin B6 in randomized clinical trials did not show any benefit (37,38).

Epidemiological studies have been performed to test the changes in the prevalence of risk factors and the adherence to the recommendations of Scientific Guidelines for risk control. The third EUROASPIRE survey was done in 2006–07 in 22 European countries to assess whether preventive cardiology had improved and if the Joint European Societies' recommendations on cardiovascular disease prevention are being followed in clinical practice (39). Data of this survey have been compared with those of the second and first EUROASPIRE surveys. Although the overall proportion of patients who smoke has remained almost the same (20.3% in EUROASPIRE I, 21.2% in II, and 18.2% in III), the proportion of women smokers aged under 50 has significantly increased. The frequency of obesity (body-mass index ⊠30 kg/m2) increased in both sexes from 25.0% in EUROASPIRE I, to 32.6% in II, and 38.0% in III (p=0.0006), as well as the frequency of self-reported diabetes mellitus which increased from 17.4%, to 20.1%, and 28.0% (p=0.004). The proportion of patients with raised blood pressure (⊠140/90 mm Hg in patients without diabetes or ⊠130/80 mm Hg in patients with diabetes) was unchanged whereas the proportion with raised total cholesterol decreased from 94.5% in EUROASPIRE I to 76.7% in II, and 46.2% in III (p<0.0001). However, while 43.3% of men have increased levels of total cholesterol in the last survey, the percentage of women with raised cholesterol is still 55.7%.

These time trends show a compelling need for more effective lifestyle management in both genders and a special effort for preventing smoking initiation and favouring smoking cessation in young women. The risk of cardiovascular diseases is indeed particularly high if smoking starts before the age of 15 (40). Furthermore, the mortality from cardiovascular diseases is higher in women who smoke than in men who smoke (41,42), even after adjustment for other risk factors. It has been shown that women metabolize nicotine faster than men, especially when taking oral contraceptives (43). Smoking and oral contraceptives exert synergistic effects on the risk of cardiovascular diseases (44). In a meta-analysis of studies on the effects of smoking cessation after myocardial infarction, mortality was reduced by 46% (Odd ratio 0.54, 95% CI 0.46-0.62), and the effect was consistent regardless of gender (45).

Mortality from cardiovascular diseases is higher in women who smoke than in men who smoke, even after adjustment for other risk factors. It has been shown that women metabolize nicotine faster than men, especially when taking oral contraceptives. Smoking and oral contraceptives exert synergistic effects on the risk of cardiovascular diseases.

Gender and blood pressure-lowering treatment

Large-scale observational studies show that lower blood pressure is associated with lower cardiovascular risk in both men and women, although some studies have suggested that different outcomes between the sexes may reflect different responses to blood pressure-lowering treatment (46-48). The trials on blood pressure-lowering treatment performed since 2006 showed that there is a fair representation of women in these studies (49-54) (see appendix 2*). Overall, 5 randomized controlled trials enrolled 69,473 patients and 28,008 were women (40.3%). Mean age of participants was 70.2 years and the mean follow-up was 3.2 years. The percentage of women enrolled in each trial varies between 27% and 60%. However, prespecified analysis by gender was present in the primary publication only in 3 of these 5 trials. No significant gender differences were found in the trials which reported the analysis separated in women and in men.

Recently, a meta-analysis of clinical trials on blood pressure-lowering treatment has been performed with the aim to quantify the effects in each sex and to determine if there are important differences in the proportional benefits of treatment between men and women (55). Thirty-one randomized trials that included 103,268 men and 87,349 women contributed to these analyses. Achieved blood pressure reductions were comparable for men and women in every comparison made. Although women experienced fewer events than men, for the primary outcome of total major cardiovascular events there was no evidence that men and women obtained different levels of protection from blood pressure-lowering or that regimens based on angiotensin-converting-enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, or diuretics/ beta-blockers were more effective in one sex than the other. Thus, all of the blood pressure-lowering regimens studied provided broadly similar protection against major cardiovascular events in men and women. Differences in cardiovascular risks between sexes are unlikely to reflect differences in response to blood pressure-lowering treatments.

These observations are similar to the results of a previous meta-analysis of randomized, controlled trials, provided by the INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) Investigators (56), and based on seven trials that included 20,802 women and 19,975 men recruited between 1972 and 1990.

The most recent Guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) released in 2007 (57) addressed the specific issue of treatment of hypertension in women. The Guidelines stated that the response to antihypertensive agents and the beneficial effects of blood pressure lowering appear to be similar in women and in men. However, the adherence to blood pressure lowering therapy is far less than ideal in both women and men. It has been shown that in Europe less than 50% of hypertensive patients are treated, and among these about 50% do not reach the level of blood pressure suggested by the Guidelines. Furthermore, the Guidelines stated that even low oestrogen oral contraceptives are associated with increased risk of hypertension, stroke and myocardial infarction. The progestogen-only pill is a contraceptive option for women with high blood pressure, but influence on cardiovascular outcomes has been insuffi ciently investigated.

The European Guidelines addressed also the important issue of hypertensive disorders in pregnancy, particularly pre-eclampsia, which may adversely affect neonatal and maternal outcomes. Recommendations on the levels of blood pressure which deserve non-pharmacological or pharmacological treatment and the specific drugs indicated in these conditions have been provided. ACE inhibitors and angiotensin receptor antagonists should be avoided in pregnant and pregnancy planning women because of potential teratogenic effects of these agents.

The recently published European Society of

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Hypertension Guidelines for blood pressure monitoring at home (58) included a chapter on the measurements in pregnant women. Home blood pressure measurement, although at present not commonly practised in this setting, has considerable potential in improving the management of pregnant women. However, few devices have been validated in pregnancy by methodologically acceptable studies.

It is also important to consider that women with previous gestational hypertension are at increased risk for cardiovascular diseases in later life (59,60). This may depend on a relative hyperandrogenic state but also on alterations in endothelial function, carbohydrate and lipid metabolism, which have been shown in otherwise healthy women with previous gestational hypertension. Accordingly, women who experienced hypertensive disorders during pregnancy should receive a strict follow-up in order to identify those who may develop hypertension later in their life.

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Diabetes and the metabolic syndrome in men and women

Since 2006 clinical trials performed in patients with diabetes enrolled a fair percentage of women, but the impact of sex differences on the reported results were rarely assessed (61-68) (see appendix 3*). Overall, 7 randomized clinical trials enrolled 48,508 patients and 20,091 were women (41.4%). Mean age of participants was 61.1 years and mean follow-up was 4.3 years. The percentage of women enrolled in each trial ranges between 30 and 59%. Four out of 7 trials (57.1%) reported the analysis of the results by gender. Existing studies, however, reveal several differences between men and women with diabetes. The risk of coronary heart disease mortality associated with diabetes is higher in women than in men. Women with diabetes, regardless of menopausal status, have a 4- to 6-fold increase in the risk of developing coronary artery disease, whereas men with diabetes have a 2- to 3-fold increase in risk (9). Furthermore, women with diabetes have a poorer prognosis after myocardial infarction and a higher risk of death from cardiovascular diseases than men with diabetes. The prevalence of the metabolic syndrome is increasing in both sexes, but has risen particularly in young women, where it is mainly driven by obesity (9).

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Furthermore, women with diabetes have a poorer prognosis after myocardial infarction and a higher risk of death from cardiovascular diseases than men with diabetes. The prevalence of the metabolic syndrome is increasing in both sexes, but has risen particularly in young women, where it is mainly driven by obesity.

Women may have an additional risk factor for developing diabetes, represented by gestational diabetes. Gestational diabetes is defined as carbohydrate intolerance of any degree that begins or is first recognised during pregnancy. The risks of gestational diabetes, which complicates about 3-5% of pregnancy, include neonatal macrosomia and increased rates of caesarean delivery (69). Moreover, it has been recently shown that gestational diabetes, as well as prepregnancy diabetes, is independently associated with perinatal depression, including new onset of postpartum depression, in low-income new mothers (70).

Additionally, the effects of gestational diabetes after pregnancy, also in the long-term, have been acknowledged (71). In fact, women with gestational diabetes are at increased risk of developing type 2 diabetes, but risk and time of onset has not been fully quantified. A recent comprehensive systematic review and meta-analysis of 20 studies that included 675,455 women and 10,859 type 2 diabetic events, has assessed the strength of association between gestational diabetes and type 2 diabetes and the effect of factors that might modify the risk (72). Women with gestational diabetes had an increased risk of developing type 2 diabetes compared with those who had a normoglycaemic pregnancy (RR 7.43, 95% CI 4.79–11.51). Thus, increased awareness of the magnitude and timing of the risk of type 2 diabetes after gestational diabetes among patients and clinicians could provide an opportunity to test and use dietary, lifestyle, and pharmacological interventions that might prevent or delay the onset of type 2 diabetes in affected women.

The 2007 Guidelines on diabetes, pre-diabetes and cardiovascular diseases of the European Society of Cardiology and the European Association for the Study of Diabetes (9) addressed the issue of diabetes and the metabolic syndrome in women. The Guidelines stated that women with glucometabolic perturbations carry a particularly high risk for cardiovascular morbidity and mortality,

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and recommend that in this respect they need special medical attention. Adequate control of blood pressure with antihypertensive agents and of cholesterol with statins have proven to be effective in reducing cardiovascular risk in both men and women with diabetes. Control of glycaemia reduces microvascular events, with a lower impact on macrovascular events, regardless of gender. Two recent trials demonstrated that even an intensive glucose control does not reduce the occurrence of major cardiovascular events and this is true for both men and women (65,66). A meta-analysis of 5 prospective randomised controlled trials of 33,040 participants (73) showed that intensive, compared with standard glycaemic control significantly reduces coronary events but not stroke.

However, women seem to be more prone to the adverse effects of some hypoglycaemic agents. A recent meta-analysis of 10 randomized controlled trials involving 13,715 participants and from 2 observational studies with 31,679 subjects showed that long-term thiazolidinediones use doubles the risk of fractures among women with type 2 diabetes, but not among men (74). A gender difference in the occurrence of adverse effects with this class of glucose-lowering agents was recently confirmed by the RECORD trial (68), in which therapy with rosiglitazone was associated with a higher incidence of distal lower limb fractures in women and not in men. Thiazolidinediones exposure was also associated with significant changes in bone mineral density at the lumbar spine and the hip. Thiazolidinediones may cause fractures by increasing adiposity of bone marrow, decreasing osteoblast activity or reducing aromatase activity which alters estrogens production and increases bone resorption. However, the underlying mechanism for the possible sex-specific effect of thiazolidinediones needs further investigation. Thus, the choice of the type of hypoglycaemic agents in women should take into consideration this potential increased risk of side effects. The recent consensus documents of the American Diabetes Association and the European Association for the Study of Diabetes advised (75) against the use of rosiglitazone and recommend caution in using the other thiazolidinediones for the risk of heart failure (76) in both men and women. They also recommend caution in their use in women because of the higher risk of fractures.

Cholesterol-lowering therapy and cardiovascular prevention in men and women

Blood cholesterol is a risk factor for cardiovascular diseases in both women and men. Statins have been demonstrated to reduce the risk of coronary artery disease and stroke in trials mainly performed in patients who already had a cardiovascular event or are at very high risk. Until recent years the evidence for a beneficial effect of statins in primary prevention, i.e. in people who did not have a cardiovascular event or are at low risk was less clear. Since 2006, six randomized clinical trials of primary or secondary prevention with statins have been performed (77-83) (see appendix 4*). A total of 50,194 patients of which 15,036 women (30%) have been enrolled and the percentage of women in each trial varies between 19% and 50%. Mean age of participants was 60.8 years and mean follow-up was 3.2 years. Of note, only one of these 6 trials reported the analysis of the results by gender in the primary publication and significant differences in the outcomes between women and men have not been shown.

A meta-analysis of data from 90,056 individuals in 14 randomized trials of secondary and primary prevention demonstrated that statin therapy can significantly and safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke, largely irrespective of the initial lipid profile (84). The absolute benefit was greater in patients at high cardiovascular risk and depended on the absolute reduction in LDL cholesterol achieved. Overall, the clinical trials included in this meta-analysis enrolled 21,575 women (24%). Although the number of events was lower in women than in men (7.3% vs. 10.6%) the benefit of statins was similar (18

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vs. 24% reduction in the events in women and men respectively, with a non-significant heterogeneity test). An updated meta-analysis published in 2009, which included also the most recent trials, confirmed these findings (85).

However, another meta-analysis which included only statins trials of primary prevention showed that the risk reduction was somewhat lower in women than in men (86). This meta-analysis was done in a population of 19,052 women and 30,194 men before the publication in 2008 of the largest trial performed with statins in individuals free of cardiovascular diseases, the JUPITER trial (82).

Statins lower cholesterol but also high-sensitivity C-reactive protein, an inflammatory biomarker that predicts cardiovascular events if its levels are increased. Accordingly, the JUPITER trial (82) was performed in 17,802 men and women without history of cardiovascular disease with normal LDL cholesterol and high-sensitivity C-reactive protein levels of 2.0 mg per litre or higher, randomized to rosuvastatin, 20 mg daily, or placebo and followed for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. It is interesting to note that in order to obtain a similar proportion of events in women and in men a different minimum age was established among the inclusion criteria. In fact, whereas the 11,001 men enrolled were 50 years of age or older, the 6,801 women were 60 years of age or older. The trial was prematurely stopped after a median follow-up of 1.9 years because of an excess of events in the placebo arm. Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval 0.46 to 0.69; P<0.00001). Consistent effects were observed in all subgroups evaluated. Specifically, the relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%). Thus, in this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. Of note, the apparent lower beneficial effect in women compared with men, observed in the previous meta-analysis, was not confirmed in this large primary prevention trial which included a number of women representing almost one third of those enrolled in all the other previous trials combined. In fact, a most recent meta-analysis on 10 trials which enrolled a total of 70,388 people without established cardiovascular disease but with cardiovascular risk factors, of whom 23,681 (34%) were women and which included the JUPITER trial, showed that statin use was associated with significantly improved survival and large reductions in the risk of major cardiovascular events in both women and men (87).

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The European Guidelines for cardiovascular disease prevention released in 2007 (33) recommend statins for men and women who had a coronary or a cerebrovascular event, and in primary prevention for men and women with high levels of LDL cholesterol or at high risk for cardiovascular diseases, i.e. diabetes. They also emphasize the role of diet and physical activity in reducing cardiovascular risk.

Aspirin for secondary and primary prevention: Do gender diff erences exist?

There is compelling evidence that aspirin reduces morbidity and mortality in patients who already had a cardiovascular event (88-89). For this reason all the Guidelines recommend the use of aspirin in patients with ischemic heart disease, cerebrovascular disease or peripheral artery disease for secondary prevention. In a recent meta-analysis of 16 secondary prevention trials involving 17,000 individuals at high average risk, the Antithrombotic Trialists' investigators (88) compared the effects of long-term aspirin versus control on myocardial infarction, stroke, or vascular death (see appendix 5*). Aspirin allocation yielded an absolute reduction in serious vascular events (6.7% vs. 8.2% per year, p<0.0001). Specifically, aspirin induced reductions in coronary events (4.3% vs. 5.3% per year, p<0.0001) and in total stroke (2.08% vs. 2.54% per year, p=0.002), with a non-significant increase in haemorrhagic stroke. These effects were similar in men and women.

The effects of aspirin in primary prevention, i.e. in subjects who did not have a cardiovascular event, are less clear. A previous meta-analysis was performed with the aim to determine if the benefits and risks of aspirin treatment in the primary prevention of cardiovascular diseases vary by sex (90). The effects of aspirin on the occurrence of myocardial infarction, stroke or cardiovascular mortality were assessed in 6 trials involving 95,456 individuals without cardiovascular disease; 3 trials included only men, 1 included only women, and 2 included both sexes. Among 51,342 women aspirin therapy was associated with a significant 12% reduction in cardiovascular events (odds ratio, 0.88; 95% confidence interval (CI), 0.79-0.99; P=0.03). This effect was driven by a 17% reduction in stroke (OR, 0.83; 95% CI, 0.70-0.97; P=0.02), which was a reflection of reduced rates of ischemic stroke (OR, 0.76; 95% CI, 0.63-0.93; P=0.008). There was no significant effect on myocardial infarction or cardiovascular mortality. Among 44,114 men aspirin therapy was associated with a significant 14% reduction in cardiovascular events (OR, 0.86; 95% CI, 0.78-0.94; P=0.01) but, at variance with the findings in women, this effect was driven by a 32% reduction in myocardial infarction (OR, 0.68; 95% CI, 0.54-0.86; P=0.001) with no significant effect on stroke or cardiovascular mortality. Aspirin treatment increased the risk of bleeding in women (OR, 1.68; 95% CI, 1.13-2.52; P=0.01) and in men (OR, 1.72; 95% CI, 1.35-2.20; P<0.001). Thus, it appears that aspirin exerts different effects in the prevention of myocardial infarction and stroke in men and women.

The most recent meta-analysis performed by the Antithrombotic Trialists' investigators (88) analyzed the same 6 trials of primary prevention, with the difference that they had access to individual participant data, which allowed the investigators to estimate the magnitude of several risk factors for selected outcomes. The overall results were similar but, at variance with the aggregate meta-analysis described above the proportional reduction in specific vascular outcomes did not differ significantly between men and women when adjustment for multiple comparisons was made.

It is interesting to note, however, that the 2009 update of the U.S. Preventive Services Task Force (USPSTF) recommendation statement encourages men age 45 to 79 years to use aspirin for the reduction in myocardial infarctions and women age 55 to 79 years for the reduction in ischemic strokes, if these effects outweigh the potential harm of an increase in gastrointestinal haemorrhages (91). It also states that the evidence is insuffi cient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older.

The 2007 Guidelines for management of ischemic stroke and transient ischemic attack of the European Stroke Organization (92) recommend low-dose aspirin for primary prevention of stroke in women aged 45 years or more who are not at increased risk for intracerebral haemorrhage and who have good gastro-intestinal tolerance, although its effect is very small.

The 2007 European Guidelines for cardiovascular

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disease prevention (33) recommend aspirin for men and women with established cardiovascular disease and diabetes, unless contraindicated. For primary prevention in asymptomatic individuals aspirin should be considered only when the 10-year risk of cardiovascular mortality is markedly increased and blood pressure well controlled, irrespective of gender.

Gender diff erences in ischemic heart disease

Clinical research on coronary heart disease since 2006 has included a lower proportion of women than their male counterpart (93-108) (see appendix 6*). Overall, 13 randomized clinical trials enrolled 90,400 patients and only 24,756 were women (27.3%). Mean age was 62.6 years and mean follow-up of the studies was 0.9 years, shorter than in the other trials because they mainly assessed the effects of treatments in the acute coronary syndromes and the outcome occurred in the first months after enrolment. The percentage of women enrolled in each trial ranges from 19.0% to 34.6% and 5/13 trials (38.4%) reported the analysis of the results by gender. Some meta-analysis of ischemic heart disease studies do not even report the number of percentage of women enrolled (109,110). However, in order to address specific issues related to coronary heart disease in women, there have been some studies conducted exclusively in women.

Clinical research on coronary heart disease since 2006 has included a lower proportion of women than their male counterpart.

Gender differences in the clinical manifestation of coronary heart disease have been shown in several studies. Women tend to present with atypical symptoms such as abdominal pain, dyspnoea, nausea and fatigue (111) more often than men. As coronary heart disease develops in women later in life than in men, the symptoms of a heart attack may be masked by other diseases (112). Furthermore, women have a higher prevalence of silent ischemia (113) and of unrecognized myocardial infarction than men (114).

A systematic review and meta-analysis of international variations across 31 Countries (115) recently assessed the prevalence of angina in men and women by using the Rose questionnaire and the myocardial infarction mortality rates from the World Health Organization. A total of 74 reports of 13,331 angina cases in women and 11,511 cases in men were included. Angina prevalence varied widely across populations, from 0.73% to 14.4% (population weighted mean 6.7%) in women and from 0.76% to 15.1% (population weighted mean 5.7%) in men. Angina prevalence showed a small female excess with a pooled random-effects sex ratio of 1.20 (95% CI 1.14 to 1.28, P<0.0001). Thus, over time and at different ages, independent of diagnostic and treatment practices, women have a similar or slightly higher prevalence of angina than men across countries with differing myocardial infarction mortality.

It has been shown that some diagnostic tests and procedures may not be as accurate in women and physicians may avoid using them leaving some women with undetected coronary heart disease, which may lead to more serious consequences for the delay in the diagnosis (116). Gender differences in the results of diagnostic testing should be taken into account in clinical practice. Exercise stress testing, commonly used to diagnose ischemic heart disease, may be less accurate in women and may give a false positive result (117-119), especially in young women with a low likelihood of coronary heart disease. However, as exercise testing carries a high negative predictive value, it is widely available and at low costs. Guidelines recommend to perform ECG stress test as first diagnostic procedure, also for women. In case of abnormal ECG stress test,

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stress echocardiography is the test with the higher sensitivity and specificity. In women not suitable for stress echocardiography or who are not able to exercise, radionuclide myocardial perfusion or MRI is a reasonable option. Cardiac CT angiography may be a useful tool for women with non-conclusive stress tests, while coronary angiography is indicated in case of abnormal or unclear non-invasive imaging tests (120).

Women with clinical findings suggestive of ischemia but without obstructive coronary artery disease on angiography represent a frequent clinical problem. In the Women's Ischemia Syndrome Evaluation (WISE) study (121) performed in women with suspected ischemia but no angiographic evidence of obstructive coronary artery disease, the 5-year cardiovascular events were 16.0% in those with a stenosis in any coronary artery of 1%-49% and 7.9% in symptomatic women with normal coronary arteries. In 1,000 asymptomatic age- and race-matched women, cardiovascular events occurred in 2.4% (P=0.002, after adjusting for baseline risk factors). Thus, women with symptoms and signs suggestive of ischemia, but without obstructive coronary artery disease, are at elevated risk for cardiovascular events compared with asymptomatic women (121). A tool for the identification of higher risk of events in this particular population of symptomatic women without obstructive coronary artery disease may be an invasive testing of coronary vasoreactivity which allows exclusion or verification of endothelial dysfunction and coronary spasm. Moreover, invasive or non-invasive determination by Positron Emission Tomography (PET) of the coronary flow reserve enables assessment of the functional status of the microvasculature, although these procedures are rarely available (120).

Women were less likely to undergo an exercise ECG test and less likely to be referred for coronary angiography.

The impact of gender on the investigation and subsequent management of stable angina and the assessment of gender differences in clinical outcome at 1 year has been analyzed in the Euro Heart Survey of Stable Angina (122). A total of 3,779 patients were included in the survey; 42% were female. Women were less likely to undergo an exercise ECG test (odds ratio, 0.81; 95% CI, 0.69 to 0.95) and less likely to be referred for coronary angiography (odds ratio, 0.59; 95% CI, 0.48 to 0.72). Antiplatelet and statin therapies were used significantly less in women than in men, both at initial assessment and at 1 year, even in those in whom coronary disease had been confirmed. Women with confirmed coronary disease were less likely to be revascularized than their male counterparts and were twice as likely to suffer death or nonfatal myocardial infarction during the 1-year follow-up period (hazard ratio, 2.09; 95% CI, 1.13 to 3.85), even after multivariable adjustment for age, abnormal ventricular function, severity of coronary disease, and diabetes. The Euroheart study showed that significant gender differences were identified in the use of investigations and of evidence-based medical therapy in stable angina. This is of particular concern in light of the adverse prognosis observed among women with stable angina and confirmed coronary disease. Further research is needed to elucidate the reasons for the adverse prognosis observed in women with stable angina and proven coronary disease.

Antiplatelet and statin therapies were used significantly less in women than in men, both at initial assessment and at 1 year, even in those in whom coronary disease had been confirmed.

Women with confirmed coronary disease were less likely to be revascularized than their male counterparts and were twice as likely to suffer death or nonfatal myocardial infarction during the 1-year follow-up period, even after multivariable adjustment for age, abnormal ventricular function, severity of coronary disease, and diabetes.

The 2006 Guidelines on stable angina of the European Society of Cardiology (123), included a chapter on the impact of the disease in women and recommended that they should have the same access to coronary angiography as men. They also stated that limited female representation in clinical trials of secondary prevention is not a justification to apply guidelines differently to women and men after diagnosis of coronary artery disease.

Acute coronary syndromes and coronary revascularization from a gender perspective

Gender differences in the manifestation of acute coronary syndromes, including ST-elevation myocardial infarction, non-ST elevation myocardial infarction and unstable angina have been demonstrated (124). As women develop coronary heart disease later than men the average age of women with non-ST-elevation-acute coronary syndromes (NSTE-ACS) was 6 years higher than in men (71 vs. 65 years) (125). As a consequence, 45% of females and 20% of males were older than 75. Diabetes was more frequent in females than in males (26 vs. 22%). Of note, in a registry of 201,114 patients (126) with a first myocardial infarction, multivariate analysis showed that younger women had a 25% higher 30-day mortality compared with men. However, gender was not an independent predictor of survival at 1-year. Interactions between age and gender observed in short-term case fatality can be explained by increased pre-hospital mortality in men. However, among older women and men, the mortality rates were similar after adjustments for co-morbid illnesses. Also in the analysis from the GUSTO-2B trial, women with NSTE-ACS had a significantly higher mortality rate at 30 days than men, but similar rates of re-infarctions (127). As for stable angina, females with NSTE-ACS are less likely to receive evidence based diagnostic procedures and therapies (128).

Recently, the benefits and risks of an early invasive strategy with coronary angiography (and if appropriate, coronary revascularization within 7 days) compared with a selective invasive strategy (with coronary angiography only if symptoms or signs of severe ischemia occurred) in women with non-ST-elevation acute coronary syndromes have been assessed in a sub-study of the OASIS-5 trial (129). There were no significant differences between the two treatment strategies in the primary outcome of death, myocardial infarction or stroke, but higher 1-year mortality and a higher rate of major bleeding at 30 days in women of the early invasive strategy group. Similarly, a meta-analysis including 2,692 women in previous randomized trials, showed no significant difference in the outcome of death or myocardial infarction, but a higher mortality with an early invasive strategy for women. Unlike in men, when combined with data from previous trials, there does not appear to be a benefit of an early invasive strategy in women with acute coronary syndromes. Another sub-study of the OASIS-5 trial, the TIMACS trial (107), showed that a very early invasive strategy (within 24 hours after randomization) did not differ from delayed intervention in preventing the primary outcome in low-risk patients, but was superior to delayed intervention in high-risk patients. The risk of events in this sub-study with early intervention was consistent in women and men. Thus, if an invasive strategy is selected for women with acute coronary syndromes, there does not appear to be harm if the intervention is performed very early in high-risk patients, similarly to what has been shown in a previous meta-analysis (130). On the basis of these somewhat conflicting results, large-scale randomized trials in women are needed in order to determine the most appropriate strategy in the management of acute coronary syndromes.

Gender differences in patients undergoing coronary revascularization procedures have been reported. Despite a higher prevalence of additional risk factors, women undergoing by-pass surgery show a similar outcome to men (131). It has been shown at cardiac catheterization that women have smaller coronary arteries (132) and that the vessel size influences device utilization for percutaneous

revascularization with a lower use of endovascular stents (133). 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 (PCI) is similar in men and women (134), as well as the effects of new antithrombotic agents as concomitant therapy and the reduction in restenosis with the wider use of drug-eluting stents (135, 136). An analysis of gender impact on outcomes in patients undergoing percutaneous coronary intervention using sirolimus-eluting stents (SES), has shown that, despite less favourable baseline clinical and angiographic features in women compared with men, the angiographic and clinical benefits of SES were similar (137). However, in European registries, women were under-treated compared with men, especially with PCI (24.4% for men vs. 22.9% for women), prescription of clopidogrel (49% for men vs. 39% for women), and prescription of GP IIb/IIIa inhibitors (24.8% for men vs. 23.8% for women) (125-128, 138-139). Referral for percutaneous or surgical revascularization was significantly lower for women. For most treatments, there was no gender differential treatment effect with new therapeutic agents (140,141). However, with GP IIb/IIIa inhibitors, several trials have reported more adverse events in women, especially in those at lower risk. Indeed, it has been shown that women experience more bleeding than men whether or not they are treated with GP IIb/IIIa inhibitors (142). As excessive dosing in women takes place frequently, it may be considered that up to one fourth of this sex-related risk difference in bleeding is avoidable. Appropriate dosing should improve care of all patients with NSTE-ACS, with a particular benefit for women.

The 2007 Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology (143) recommend that women be evaluated and treated similarly to men, with special attention to comorbidities. The 2008 Guidelines for the Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation (144) did not include any specific recommendation related to gender.

Gender differences in heart failure

Heart failure is the most common cardiovascular cause of hospital admission in both men and women. However, gender differences in the manifestation of heart failure have been demonstrated (145). More men than women suffer from heart failure at younger ages, but after the age of 75 the reverse is true, as more women are affected by heart failure, especially with normal left ventricular ejection fraction (146). With the increase of life expectancy, which is greater in women than in men, the proportion of older women with heart failure is expected to increase further in the future.

More men than women suffer from heart failure at younger ages, but after the age of 75 the reverse is true, as more women are affected by heart failure, especially with normal left ventricular ejection fraction.

With the increase of life expectancy, which is greater in women than in men, the proportion of older women with heart failure is expected to increase further in the future.

In the past, most large, multicenter trials have not included sufficient numbers of women to allow for conclusions on the efficacy and safety of their treatment. Since 2006 the proportion of women enrolled in clinical trials on heart failure did not significantly increase (147-161) (see appendix 7*). Overall 11 randomized clinical trials enrolled 46,141 patients and 12,834 were women (27.8%). Mean age was 69.2 years and mean follow-up 2.4 years. The percentage of women enrolled in each trial ranges from 15% to 60%. Despite this variable proportion of women, the majority of the trials (8/11; 72.7%) reported the analysis of the results by gender.

The analysis of previous trials suggested gender differences in the efficacy of some therapeutic agents. A post-hoc analysis of the DIG trial showed that women with heart failure who received digoxin

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had a higher mortality than those receiving placebo (162), an effect that was not observed in men and that may depend on a higher percentage of women with drug plasma levels above the therapeutic range due to a lower renal clearance of digoxin (163). It has also been suggested that women with heart failure, particularly with asymptomatic reduced left ventricular ejection fraction (LVEF), may not show survival benefits from ACE inhibition (164,165). Women may also have a different safety profile than men, as evidenced by their higher risk of ACE inhibitors-induced cough (165). However, in the most recent trials which reported the results by gender, the effects of main interventions were similar in men and women with heart failure. The recent MADIT-CRT trial demonstrated that cardiac resynchronization therapy combined with ICD decreased the risk of heart-failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex and that the beneficial effect was significantly greater in women than in men (167).

There are studies that have assessed the association between gender and clinical characteristics, outcome and management of heart failure. An analysis from 8,791 men and 2,851 women with systolic dysfunction, randomized in 5 clinical trials (168), showed that, irrespective of aetiology, women were older, smoked less often or had prior myocardial infarctions, but had higher systolic blood pressures, more diabetes, and more severe symptoms than men. However, women had better outcomes (all-cause mortality or all-cause hospitalization) than men. Similar results in terms of outcomes have been obtained with an analysis of 2,400 women and 5,199 men randomized in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme (150). This trial enrolled also heart failure patients with a normal ejection fraction that was more frequent in women (50%) than in men (35%). An ischemic cause of heart failure was less frequent in women (51%) than in men (67%). All-cause mortality was 21.5% in women and 25.3% in men and fewer women (30.4%) than men (33.3%) experienced cardiovascular death or heart failure hospitalization, independently of LVEF or aetiology of heart failure.

The Euroheart Survey on heart failure performed in Europe (169) found that among a total of 8,914 patients (47% women) with confirmed diagnosis of heart failure, women were older (74.7 vs. 68.3 years, $p<0.001$), less often had evidence of coronary artery disease (56% vs. 66%), were more likely to have hypertension, diabetes, or valvular heart disease. However, at variance with the randomized trials, in this survey which reflects the clinical practice, 12-week mortality was similar for men and women. Indeed, gender differences in the management of heart failure may have contributed to influence the outcome. In fact, fewer women had an investigation of left ventricular function (59% vs. 74%, age-adjusted OR 0.67; 95% CI 0.61 to 0.74) and were treated with drugs with a documented impact on survival, that is ACE-inhibitors and beta-blockers (OR 0.72; 95% CI 0.61 to 0.86 and OR 0.76; 95% CI 0.65 to 0.89, respectively). Furthermore, an observational study on 13,034 patients with heart failure and left ventricular ejection fraction < 30%, reported that among potentially eligible patients, fewer women than men received implantable cardioverter-defibrillator (ICD) therapy (170). Thus, women with heart failure appear to be less often investigated and treated with evidence-based drugs, even after adjustment for age and important clinical characteristics.

Women with heart failure appear to be less often investigated and treated with evidence-based drugs, even after adjustment for age and important clinical characteristics.

The 2008 Guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (171) do not include gender related issues. However, they provide a recommendation for pregnancy, stating that this condition may lead to deterioration of heart failure due to the rise in blood volume and increase in cardiac output, as well as the substantial increase in extra vascular fluid. Importantly, many medications used in heart failure treatment are contra-indicated during pregnancy. As the risk

of pregnancy is considered greater than the risks linked to contraceptive use, it is recommended that women with heart failure discuss contraceptives and planned pregnancy with a physician in order to take an informed decision based on assessment of potential risks.

Gender and atrial fibrillation

Atrial fibrillation is the most common arrhythmia encountered in clinical practice, accounting for approximately one third of all hospitalizations for cardiac rhythm disturbances (172). The prevalence of atrial fibrillation is 0.4% to 1% in the general population (173), and increases with age to 8% in patients older than 80 (174). The median age of patients with atrial fibrillation is about 75 years, but approximately 60% of those over 75 are female. In a large cohort of 34,221 initially healthy women participating in the Women's Health Study (174) blood pressure, especially systolic blood pressure, was strongly associated with incident atrial fibrillation.

Atrial fibrillation is associated with an increased long-term risk of stroke (172,176), heart failure, and all-cause mortality, especially among women (172). The Stroke Prevention in Atrial Fibrillation (SPAF) study (177), and the Framingham study (178) found that women with atrial fibrillation are at greater risk of stroke, but antithrombotic therapy is equally effective in both genders (179).

Atrial fibrillation is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality, especially among women.

Clinical trials on the treatment of atrial fibrillation and on the prevention of stroke enrolled a fair proportion of women (180-188) (see appendix 8*). Overall, 7 randomized clinical trials enrolled 28,790 patients of which 10,618 were women (36.9%). The mean age was 69.0 years and the mean follow-up 2.3 years. The percentage of women enrolled in each trial ranges from 23.3% to 56.6% and 3/7 trials (42.8%) reported the analysis of the results by gender. No gender differences in the outcomes have been observed.

Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation have been demonstrated in Europe. A report from the Euro Heart Survey on atrial fibrillation (189) in 5,333 patients (42% female) showed that compared with men, women were older, had a lower quality of life (QoL), had more comorbidities, more often had heart failure with preserved left ventricular systolic function (18% vs. 7%, $p<0.001$), and less often had heart failure with systolic dysfunction (17% vs. 26%, $p<0.001$). Among patients with typical atrial fibrillation symptoms (56% of women, 49% of men), there was no gender-related difference in the choice of rate or rhythm control. Among patients with atypical or no symptoms (44% of women, 51% of men), women less frequently underwent rhythm control (39% vs. 51%, $p<0.001$) than did men. Women underwent less electrical cardioversion (22% vs. 28%, $p<0.001$). Prescription of oral anticoagulants was identical (65%) in both genders, although women showed a higher prevalence of additional risk factors for stroke, as indicated by higher CHADS2 scores. One-year outcome was similar, except that women had a higher chance for stroke, independent of age and additional risk factors (odds ratio 1.83 in multivariable regression analysis, $p=0.019$). Thus, women with atrial fibrillation in the European countries had more comorbidities, a lower QoL, and a higher risk for stroke than men.

Women have a greater risk of developing adverse drug reactions than men. In fact, female prevalence is higher than expected among patients with torsades des pointes induced by drugs which prolong ventricular repolarization and a review

* Available on-line on http://www.ehnheart.org/content/ItemPublication.asp?docid=7441&level0=1456&level1=2096&level2=2100

of reported cases of cardiovascular drug-related torsades des pointes showed a female prevalence of 70% (190). Among patients who received d-l sotalol, a drug used for both restoring and maintaining sinus rhythm in atrial fibrillation, torsades des pointes developed in 1.9% of males and in 4.1% of females (191). Furthermore, in the Sportif V trial women were more prone to anticoagulant-related bleeding and to higher rate of thrombo-embolism due to more frequent interruption of anticoagulant therapy (192).

The 2006 European Society of Cardiology Guidelines for the management of patients with atrial fibrillation (172) addresses the gender issues. They define female gender as an additional risk factor for stroke, especially in patients over the age of 75 and recommend antithrombotic therapy with either aspirin or a vitamin K antagonist for prevention of thromboembolism. They also include female gender as a risk factor for frequent recurrence of paroxysmal atrial fibrillation and for drug-induced ventricular arrhythmias.

Gender differences in stroke

Stroke is a major cause of death in both men and women and represents the first cause of disability and the second cause of dementia (1,2). Several risk factors for ischemic heart disease increase also the predisposition for stroke. Accordingly, the identification of patients at risk and the correction of risk factors is the basis of prevention of both ischemic heart disease and stroke. However, approximately 20% of stroke is not explained by the presence of traditional risk factors and it has been hypothized that genetic factors may play a role. It has recently been shown that heritability of ischemic stroke is greater in women than in men, with an excess of affected mothers and affected sisters in female probands, independent of traditional vascular risk factors (193).

Clinical trials on the treatment of stroke enrolled a fair proportion of women (194-207) (See appendix 9*). Overall 10 randomized clinical trials enrolled 28,790 patients and 10,618 were women (36.9%). Mean age of participants was 69 years and mean follow-up was 1.26 years, as the majority of trials have been performed in the acute phase of stroke. The percentage of women enrolled in each trial ranges from 25% to 52% and 5/10 trials (50%) reported the analysis of the results by gender.

Gender differences in the clinical presentation and outcome of stroke have been demonstrated. In the Framingham Study (208) 5,119 individuals (2,829 women) and 4,957 offspring (2,565 women) were followed to first incident stroke. Among the 1,136 incident strokes (638 in women) over 5.6 years of follow-up women were significantly older (75.1 vs 71.1 years for men; P<0.001) at their first-ever stroke, had a higher stroke incidence above the age of 85, and a higher lifetime risk of stroke at all ages. There was no significant difference in stroke subtype, stroke severity, and case fatality rates between genders. Women were significantly (P<0.01) more disabled in the acute phase, at 3 to 6 months after stroke and 3.5 times more likely to be institutionalized (P<0.01). These results support the existence of gender-differences in stroke incidence, lifetime risk of stroke, age at first stroke, post stroke disability, and institutionalization rates.

It has been shown that gender differences in clinical management after an acute stroke also exist.

It has been shown that gender differences in clinical management after an acute stroke also exist (2,209,210). A multicenter study conducted in 7 European countries (210) showed that after an acute cerebrovascular event, brain imaging, Doppler examination, echocardiogram, and angiography were significantly less often performed in female than in male patients. Furthermore, there is evidence that women, especially of older age, are less likely to receive lipid lowering drugs and antithrombotics for secondary prevention of stroke (211).

Thrombolytic therapy is the only approved intervention for acute ischemic stroke. A meta-analysis showed that women benefit more than

* Available on-line on http://www.ehnheart.org/content/ItemPublication.asp?docid=7441&level0=1456&level1=2096&level2=2100

men from this therapy (212). The beneficial effect of thrombolytic therapy is particularly evident when administered early after the onset of symptoms but two recent studies demonstrated that this therapy is effective also after 3 hours from the onset of symptoms, if administered within 4.5 hours (201,213). However, the metabolic syndrome, which is more prevalent in women, confers a higher resistance to intravenous thrombolysis in acute middle cerebral artery ischemic stroke and this effect appears to be more pronounced in women than in men (214).

Intra-arterial thrombolysis is equally effective to intravenous thrombolysis, but the therapeutic window is extended to 6 hours from the onset of symptoms. In the PROACT-2 study of intra-arterial stroke thrombolysis (196), women showed a larger treatment effect (20% absolute benefit) compared with men (10% absolute benefit). The reason for this interaction is probably that thrombolytic treatment nullifies the worse outcome for untreated women compared with men.

Despite the greater effi cacy in women of thrombolytic therapy, the percentage of women who do not receive rt-PA after acute ischemic stroke is higher compared to men.

However, despite the greater effi cacy of thrombolytic therapy, the percentage of women who do not receive rt-PA after acute ischemic stroke is higher compared to men. A meta-analysis to determine whether a sex disparity existed, showed that women had a 30% lower probability of receiving rt-PA treatment than men (215). Further studies to explore the origins of this sex disparity are warranted. Thrombolytic therapy after stroke should be administered within the first 3-4.5 hours after the onset of symptoms, since after this period the risk of bleedings outweighs the benefit of treatment. The percentage of women who reach the hospital within this time period is lower than that of men and this observation may partially explain the under-treatment of women with thrombolytic therapy (210). Among 1,922 acute stroke cases who presented in 15 hospitals participating in a state-wide stroke registry (216), women were significantly less likely than men to present with any stroke warning sign or suspected stroke (87.5% versus 91.4%). In adjusted analyses, women had 11% longer door-to-doctor intervals and 15% longer door-to-image intervals. Furthermore, these gender differences remained evident after restricting to patients who arrived within 6 or within 2 hours of symptom onset. Thus, women with acute stroke experienced greater delays in an emergency department than men, which were not attributable to differences in presenting symptoms, time of arrival, age, or other confounders.

The 2008 Guidelines for management of ischemic stroke and transient ischemic attack of the European Stroke Organization (92) included gender issues in the text but they recommend the same management and treatment for women and men. The only gender-specific recommendation is on the use of aspirin for the primary prevention of stroke in women and not in men, as mentioned before.

Conclusions

Cardiovascular diseases are the leading cause of mortality in women and in men (1). Coronary heart disease represents the majority of deaths in both genders, whereas stroke is a relatively more frequent cause of death in women than in men (2). Despite this unequivocal epidemiological observation, confirmed by the data released by the WHO in 2008, the cardiovascular risk in females is underestimated because women are perceived to be protected against cardiovascular diseases (217). However, the prevalence of cardiovascular diseases in women is lower than in men during the fertile age but it increases after menopause. The misperception of the actual risk in this period may leave most women without appropriate preventive measures (2). Furthermore, the clinical manifestations of ischemic heart disease in women may be different from those commonly observed in men, thus leading to a delay in the diagnosis (217).

Under-representation of women in clinical trials performed in the past has been clearly demonstrated. The European scientific societies and the foundations involved in the field of cardiovascular diseases have taken initiatives to increase the representation of women in cardiovascular research. European institutions, national research authorities and regulatory agencies have been involved in increasing efforts to enrol a larger number of women in clinical trials.

One of the objectives of the EuroHeart project (WP6) was to assess the representation of women in cardiovascular research in Europe in the last years. The search was conducted in order to identify publications (European or international with European representation) of observational/ epidemiological studies, randomized clinical trials, meta-analyses, which enrolled women and men or women only, European registries, Guidelines and Statements of European Scientific Societies. Studies that did not involve European subjects were not considered. The number and percentage of women enrolled in the studies, age of participants, time of follow-up, availability of the analysis of outcomes by gender, identification of gender differences in risk, outcome or clinical practice, and inclusion of gender issues in the European scientific guidelines have been considered.

The analysis has been performed specifically on studies focused on the evaluation of cardiovascular risk, management of menopause and hormone replacement therapy, blood pressure and lipid lowering interventions, diabetes, antithrombotic therapies, clinical management and treatment of ischemic heart disease, heart failure, atrial fibrillation and stroke.

Overall, the 62 randomized clinical trials published since 2006 and analyzed here (table 1), enrolled 380,891 participants and 127,716 were women (33.5%) (Figure 1 and 2). Mean age of participants was 66.3 years (figure 3) and mean follow-up 2.7 years (figure 4). The percentage of women enrolled in each trial ranges from 15% to 60%, but only 31/62 trials (50%) reported the analysis of the results by gender (figure 5).

However, the representation of women in the clinical trials is not homogeneous. Trials performed on blood pressure-lowering therapies, diabetes, atrial fibrillation and stroke enrolled a higher proportion of women (aproximatively 40%) but the results by gender were reported only in about half of the trials. Trials performed on cholesterol-lowering therapy and on management and treatment of ischemic heart disease and heart failure have enrolled the lowest proportion of women (about 30%). The number of trials which reported the results according to gender varied from 82% in the heart failure trials to the extremely low figure of 18% (1 of 6) for trials on cholesterol-lowering therapy.

Despite an increase in the number and proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischemic heart disease and heart failure, which may have affected the reliability of subgroup analysis. Furthermore, approximately 50% of the trials did not report an analysis of the results by gender, and this occurred also for studies which enrolled a large number of men and women. The duration

of follow-up may have influenced the number of events in women when compared with those occurring in men, as females of the same age as males may be at lower risk at the time of enrolment. This difference should be taken into account in the design of a clinical trial. One of the reasons of a lower enrolment of women in clinical trials is indeed the lower occurrence of outcomes in females, which may affect the costs of the study. This apparent conflict between adequate enrolment of women and cost-effective trial execution may be overcome by a more accurate choice of the inclusion criteria. A positive example comes from the recent JUPITER trial of primary prevention with statins, where men over the age of 50 and women over the age of 60 have been enrolled.

The reason of the under-representation of females in cardiovascular research may also be partly explained by a lower willingness of women to be enrolled, due to their misperception of risk of cardiovascular diseases. Another explanation might be the difficulties in terms of transportation or support for the follow-up visits. Barriers to the enrolment of women in clinical trials should therefore be removed in order to increase the proportion of women studied.

Most of the clinical trials and meta-analyses on cardiovascular diseases analyzed here, did not report a significantly lower efficacy of interventions in women compared with men. For some therapies there is even a suggestion of greater efficacy in women than in men, as in the case of cardiac resynchronization therapy in heart failure or thrombolysis after ischemic stroke. Accordingly, Scientific Guidelines do not generally provide specific recommendations for prevention or treatment in women.

The studies which reported some gender differences are those on primary prevention with aspirin in individuals without signs of cardiovascular disease. Although the benefit of this therapy is modest in both asymptomatic men and women, it appears that aspirin reduces the risk of coronary heart disease in men and of stroke in women. However, other factors, such as the overall risk of cardiovascular mortality, the risk of bleedings and age, rather than gender, should influence the choice of this antithrombotic therapy.

Another finding is the greater occurrence of adverse effects of drugs and procedures in women than in men. This effect has been observed in diabetic women treated with thiazolidinediones who experienced an excess of bone fractures, as opposed to their male counterpart, or in the treatment of acute coronary syndromes where women appear to be more prone to bleedings.

Finally, in some areas, clinical trials provided somewhat conflicting results in women, as in the assessment of the efficacy of early invasive strategies in acute coronary syndromes. In this case only the design of large-scale randomized trials in women may contribute to determine the most appropriate strategy for management and treatment.

The Statement of the Policy Conference on Cardiovascular Diseases in Women in 2006 (2) provided priorities and recommendations for the improvement of risk stratification, diagnosis and treatment of cardiovascular diseases in women. Although some improvement in this field has occurred, it is still extremely urgent to collect epidemiological data for cardiovascular diseases and risk factors in women of different age groups in Europe in order to improve the accuracy of risk charts to predict the risk of cardiac events in females (2). Moreover, it is necessary to tailor the risk assessment process to incorporate risk factors that are particularly important for women, i.e. diabetes, obesity and smoking and extend risk assessment to older age groups in order to account for the delayed onset of cardiovascular diseases in women (2). The assessment of the predictive value of diagnostic procedures by gender should be encouraged and the implementation of the recommendations of clinical guidelines with respect to the adoption of preventive measures and optimal medical therapy in women should be promoted (2). The recommendation on cardiovascular research in women of the Policy Conference released in 2006

(2) should be followed and implemented. Although non prespecified, post-hoc, subgroup analysis by gender for already completed clinical trials with adequate power and representation of women may help to explore the issue of gender differences, clinical trials enrolling only female patients or clinical trials enrolling a significant proportion of women to allow for prespecified gender analysis should be conducted (2).

Educational activities to increase awareness about morbidity and mortality related to cardiovascular diseases in women should be implemented and targeted to different audiences including health care professionals, the medical community, the stakeholders in this field and also the general population.

Initiatives which contribute to increase the awareness in Europe that cardiovascular diseases are the major cause of death in women and to improve the knowledge of risk factors, presentation and treatment of cardiovascular diseases in women should be encouraged. Scientific societies, patients' associations and foundations should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on sex and gender issues in cardiovascular medicine. Furthermore, a larger representation of women in clinical trials should increase the understanding of gender differences in the response to drug therapy and specific gender-related recommendations for prevention, management and treatment of cardiovascular diseases could be provided in the future where possible.

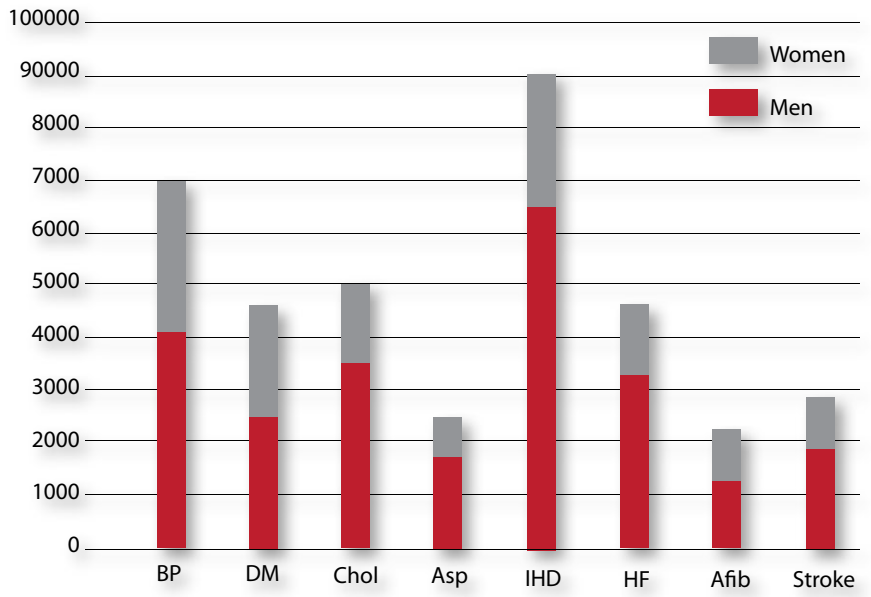
Table and Figures

Table 1 - Clinical trials

This table contains a summary of the 62 randomised clinical trials published since 2006 and analysed in this report. More detailed information on each of the topics can be found in the appendices which form an integral part of this report. These appendices can be consulted on-line on http://www.ehnheart.org/content/ItemPublication.asp?docid=7441&level0=1456&level1=2096&level2=2100

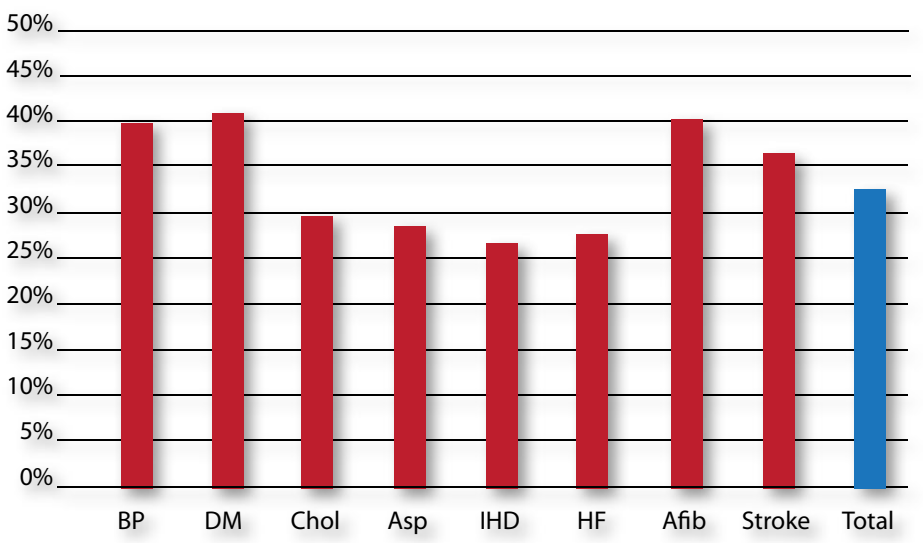
TOPICS	NUMBER OF PARTICIPANTS	NUMBER OF WOMEN	PERCENTAGE OF WOMEN	MEAN AGE	MEAN FOLLOW-UP (YEARS)	TRIALS WITH ANALYSIS BY GENDER N, (%)
BLOOD PRESSURE-LOWERING TREATMENT	69,473	28,008	40.3%	70.2	3.2	3/5 (60%)
DIABETES AND METABOLIC SYNDROME	48,508	20,091	41.4%	61.1	4.3	4/7 (57.1%)
CHOLESTEROL-LOWERING THERAPY	50,194	15,036	30.0%	60.8	3.2	1/6 (16.7%)
ANTITHROMBOTIC THERAPY AND OTHER INTERVENTIONS	24,874	7,181	28.9%	65.3	3.4	2/3 (66.7%)
ISCHAEMIC HEART DISEASE	90,400	24,756	27.3%	62.6	0.96	5/13 (38.4%)
HEART FAILURE	46,141	12,834	27.8%	69.2	2.4	8/11 (72.7%)
ATRIAL FIBRILLATION	22,511	9,192	40.8%	72.1	2.5	3/7 (42.8%)
STROKE	28,790	10,618	36.9%	69.0	1.26	5/10 (50%)
TOTAL	380,891	127,716	33.5%	66.3	2.7	31/62 (50.0%)

Figure 1 - Participants in clinical trials by gender



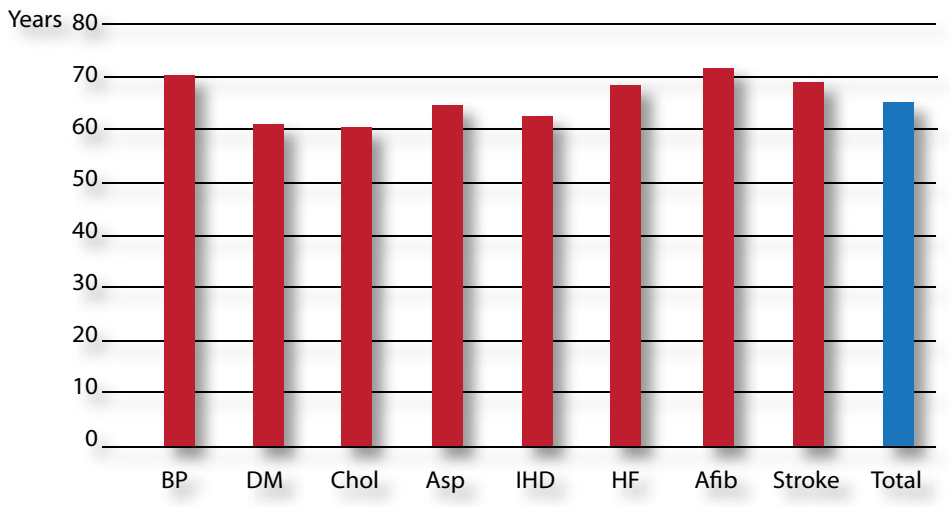
BP: blood pressure; DM: diabetes mellitus; Chol: cholesterol; Asp: aspirin; IHD: ischemic heart disease; HF: heart failure; Afib: atrial fibrillation.

Figure 2 - Percentage of women in clinical trials



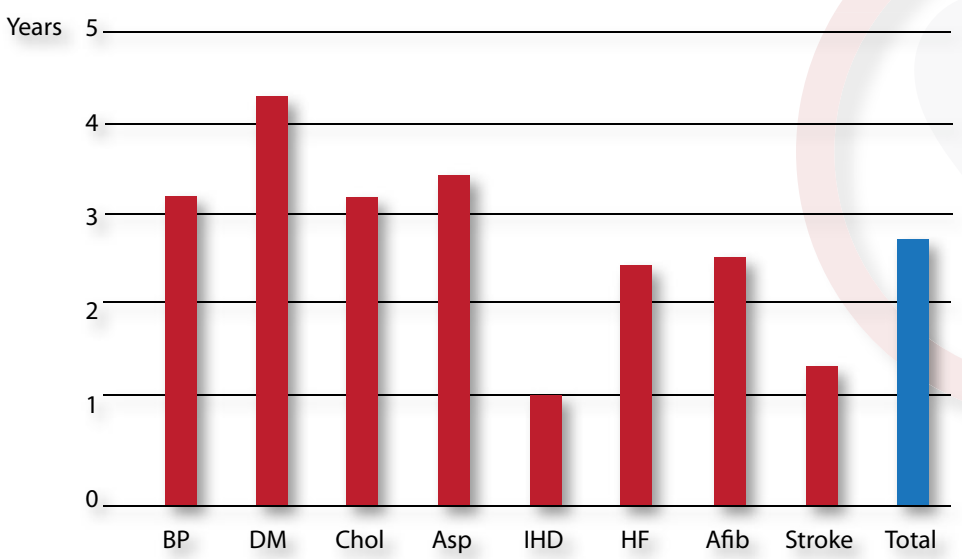
BP: blood pressure; DM: diabetes mellitus; Chol: cholesterol; Asp: aspirin; IHD: ischemic heart disease; HF: heart failure; Afib: atrial fibrillation.

Figure 3 - Mean age of participants in clinical trials



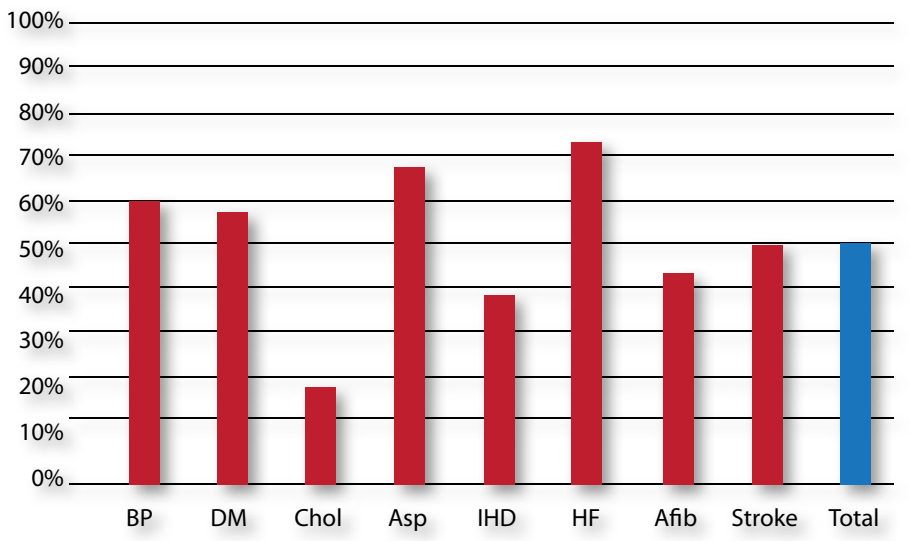
BP: blood pressure; DM: diabetes mellitus; Chol: cholesterol; Asp: aspirin; IHD: ischemic heart disease; HF: heart failure; Afib: atrial fibrillation.

Figure 4 - Mean follow-up of clinical trials



BP: blood pressure; DM: diabetes mellitus; Chol: cholesterol; Asp: aspirin; IHD: ischemic heart disease; HF: heart failure; Afib: atrial fibrillation.

Figure 5 - Clinical trials with analysis by gender



BP: blood pressure; DM: diabetes mellitus; Chol: cholesterol; Asp: aspirin; IHD: ischemic heart disease; HF: heart failure; Afib: atrial fibrillation.

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