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CURRENT OPINION

Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project

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Introduction

Cardiovascular diseases represent the major cause of mortality in women and in men.[1,2] However, gender differences in the clinical presentation of cardiovascular diseases have been demonstrated[3] and some therapeutic options may not be equally effective and safe in men and women.[4] Furthermore, gender differences in pharmacokinetics and pharmacodynamics may contribute to a different response to cardiovascular drugs in women when compared with men.[5,6] Accordingly, preventive and therapeutical interventions should be tested in populations that fairly represent the gender distribution. In contrast, under-representation of women in cardiovascular trials has been clearly demonstrated in the past.

The European Heart Health Strategy (EuroHeart) project of the European Society of Cardiology (ESC) and the European Heart Network (EHN), co-funded by the European Commission, addressed the issue of women representation in cardiovascular clinical research in Europe.

Under-representation of women in clinical trials

The enrolment of women in cardiovascular clinical trials funded by the NHLBI was 38% between 1965 and 1998[7] and 27% between 1997 and 2006.[8] Furthermore, only 13 of 19 studies reported gender-based outcomes.

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

In 2005, the European Medicines Agency and the ESC Policy Conference on Cardiovascular Diseases in Women recommended a significant representation of women in clinical trials.[3]

The current representation of women in European cardiovascular research has been assessed in the EuroHeart project. Observational studies; randomized clinical trials, including meta-analyses; European registries; Guidelines and Statements of European Scientific Societies, published between 2006 and June 2009, have been analysed, focusing on the number and percentage of women enrolled, age of participants, time of follow-up, availability of the analysis of outcomes by gender, identification of gender differences in risk, and outcome or clinical practice.

Smoking among young women and risk of cardiovascular diseases

The 2006 EUROASPIRE III survey[9] has shown that although the overall percentage of smokers has remained nearly the same, the proportion of women smokers aged less than 50 years has significantly increased, suggesting a compelling need for a special effort to prevent smoking initiation and favour smoking cessation in young women. The risk of cardiovascular disease is particularly high if smoking starts before the age of 15 years.[10] Furthermore, the mortality from cardiovascular disease is higher in women than in men who smoke, even after adjustment for other risk factors.[10] Women metabolize nicotine faster than men, especially when taking oral contraceptives.[10] Smoking and oral contraceptives exert synergistic effects and increase the risk of myocardial infarction particularly in young women.[10] A meta-analysis on the effects of smoking cessation after myocardial infarction showed that mortality was reduced by 46% in both men and women.[10]

Gender and blood pressure-lowering treatment

A lower blood pressure is associated with lower cardiovascular risk in both men and women.[11] Since 2006, the five randomized trials on blood pressure-lowering therapy[12–16] enrolled 69 473 patients and 28 008 were women (40.3%, range 27–60%)

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(*Figures 1* and *2*). The mean age of participants was 70.2 years (*Figure 3*) and the mean follow-up was 3.2 years. However, analysis by gender was present in three of the five trials (60%). No significant gender differences have been found.

A meta-analysis on blood pressure-lowering treatment[17] showed that for the primary outcome of total major cardiovascular events, there were no gender differences.

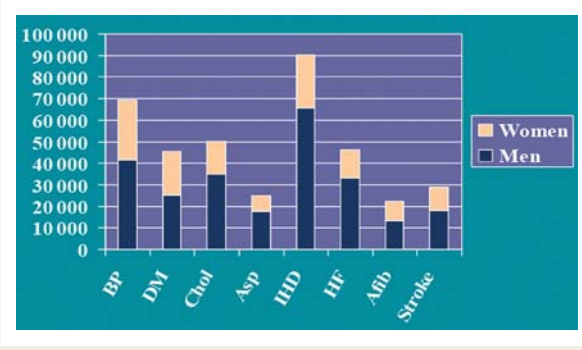

Figure 1 Participants in clinical trials by gender. BP, blood pressure; DM, diabetes mellitus; Chol, cholesterol; Asp, aspirin; IHD, ischaemic heart disease; HF, heart failure; Afib, atrial fibrillation.

Figure 2 Percentage of women in clinical trials. Abbreviations as in *Figure 1*.

Figure 3 Mean age of participants in clinical trials. Abbreviations as in *Figure 1*.

The 2007 ESC and European Society of Hypertension (ESH) Guidelines on hypertension[18] stated that the benefit of blood pressure lowering is similar in women and in men. Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-receptor antagonists should be avoided in pregnant and pregnancy planning women because of potential teratogenic effects. Women with previous gestational hypertension are at increased risk for cardiovascular disease in later life and should receive a strict follow-up. The ESH Guidelines for blood pressure monitoring at home[19] stated that this type of measurement has considerable potential in improving the management of pregnant women.

Diabetes and cardiovascular risk in men and women

Since 2006, the seven randomized trials on diabetes[20–26] enrolled 48 508 patients and 20 091 were women (41.4%, range 30–59%) (*Figures 1* and *2*). The mean age of participants was 61.1 years (*Figure 3*), the mean follow-up was 4.3 years, and four of the seven trials (57.1%) reported the analysis of the results by gender.

Women with diabetes have a higher risk than men of developing coronary artery disease or stroke, a poorer prognosis after myocardial infarction, and a higher risk of cardiovascular death.[27] Furthermore, a meta-analysis[28] showed that women with gestational diabetes have an increased risk of developing diabetes. Thus, interventions that might prevent or delay the onset of diabetes in affected women should be considered.

The 2007 ESC and European Association for the Study of Diabetes (EASD) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases[27] recommend special medical attention in diabetic women. Blood pressure and cholesterol control is effective in reducing cardiovascular risk in both men and women with diabetes. Glucose control, even if intensive, reduces microvascular events, with a lower impact on macrovascular events, regardless of gender.[23,24,29]

Women are more prone to the adverse effects of newer hypoglycaemic agents. A meta-analysis showed that thiazolidinediones double the risk of fractures among diabetic women, but not among men,[30] a finding confirmed by the RECORD trial.[26] The EASD and American Diabetes Association consensus document[31] advised against the use of rosiglitazone and recommends caution in using other thiazolidinediones for the risk of heart failure[29] in both genders and for the higher risk of fractures in women.

Cholesterol-lowering therapy and cardiovascular prevention in men and women

Since 2006, a total of 50 194 patients of which 15 036 women (30%, range 19–50%) (*Figures 1* and *2*) have been enrolled in six clinical trials on statins.[32–38] The mean age of participants was 60.8 years (*Figure 3*) and the mean follow-up was 3.2 years. Of note, only one trial (16.6%) reported the analysis of the results by gender.

A meta-analysis, recently updated,[39,40] demonstrated that statins reduce cardiovascular events in both men and women. 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.[41] Recently, the JUPITER trial[37] performed in subjects without a history of cardiovascular disease with normal LDL and high-sensitivity C-reactive protein, a biomarker of inflammation, showed that cardiovascular events were significantly reduced by rosuvastatin in both men and women. Of note, to obtain a fair proportion of events also in women, a different minimum age was established among the inclusion criteria, 50 years for men and 60 for women. Thus, the apparent lower benefit of statins in primary prevention of women has not been confirmed in this large trial, as well as in a most recent meta-analysis.[42]

The 2007 European Guidelines for cardiovascular disease prevention[10] recommend statins for men and women who had a cardiovascular event, and in primary prevention in the case of high levels of LDL cholesterol or in subjects at high risk for cardiovascular disease.

Aspirin for secondary and primary prevention: are there gender differences?

A recent meta-analysis[43] confirmed that aspirin is beneficial in both men and women who already had a cardiovascular event.

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[44] showed that in women, aspirin reduced stroke but not myocardial infarction, whereas in men, it reduced myocardial infarction but not stroke. However, when adjustment for multiple comparisons was made in the most recent meta-analysis,[43] the reduction in vascular outcomes did not differ between men and women.

Of note, the 2009 USPSTF recommendation statement encourages men aged 45–79 years to use aspirin to reduce myocardial infarctions and women aged 55–79 years to reduce ischaemic strokes.[45]

The 2008 European Stroke Organization (ESO) Guidelines on ischaemic stroke[46] recommend aspirin for primary prevention of stroke in women aged 45 years or more.

The 2007 European Guidelines for cardiovascular disease prevention[10] stated that in asymptomatic individuals, aspirin should be considered only when the 10-year risk of cardiovascular mortality is markedly increased, irrespective of gender.

Gender differences in ischaemic heart disease

Overall, the 13 randomized trials on ischaemic heart disease[47–59] enrolled 90 400 patients and only 24 756 were women (27.3%, range 19–34.6%) (*Figures 1* and *2*). The mean age was 62.6 years (*Figure 3*) and the mean follow-up was 0.9 years, shorter than in the other trials because they mainly assessed the effects of treatments in the acute coronary syndromes (ACS) and the outcome occurred in the first months after enrolment. Five of the 13 trials (38.4%) reported the analysis of the results by gender.

Women with clinical findings suggestive of ischaemia but without obstructive coronary artery disease on angiography represent a frequent clinical problem. The WISE study[60] showed that women with suspected ischaemia but no angiographic evidence of obstructive coronary artery disease are at elevated risk for cardiovascular events compared with asymptomatic women.[60] In the case of normal angiography, an invasive testing of coronary vasoreactivity or the determination by PET of the coronary flow reserve, although rarely available, may help the identification of women at risk.[61,62]

The EuroHeart Survey of Stable Angina[63] in 3779 patients (42% women) showed that less women than men underwent exercise ECG test or coronary angiography and received revascularization, antiplatelet, and statin therapies. Death or non-fatal myocardial infarction occurred more often in women during the 1-year follow-up, even after adjustment for age and other factors. Further research is needed to elucidate the reasons of these findings.

The 2006 ESC Guidelines on angina[64] recommend that women should have equal access to coronary angiography and treatment as men.

Acute coronary syndromes and coronary revascularization from a gender perspective

Gender differences in the manifestation of ACS have been demonstrated.[3] Women with non-ST-elevation-ACS (NSTE-ACS) are older than men[3] and this may partly explain the less frequent reporting of chest pain.[65] In a registry of 201 114 patients with myocardial infarction,[66] younger women had a higher 30-day mortality compared with men. However, gender was not an independent predictor of survival at 1-year and among older women and men, mortality was similar after adjustments for co-morbidities. As for stable angina, females with NSTE-ACS are less likely to receive evidence-based diagnostic procedures and therapies.[67]

The effects of an early invasive strategy with coronary angiography and a selective invasive strategy (with coronary angiography only if symptoms or signs of severe ischaemia occurred) in women with NSTE-ACS[68] did not differ in the primary outcome of death, myocardial infarction, or stroke. However, a higher 1-year mortality and a higher rate of major bleeding at 30 days were observed in women of the early invasive strategy group.[68,69] An early invasive strategy did not differ from delayed intervention in low-risk patients, but was superior in high-risk patients in both genders.[59,69] Randomized trials enrolling a large number of women are needed to determine the most appropriate strategy in the management of ACS.

The risk of adverse events during and after percutaneous coronary revascularization (PCI) is greater in women than in men, although the success rate is similar, as well as the effects of antithrombotic agents.[3] Despite less favourable baseline clinical and angiographic features in women compared with men, the angiographic and clinical benefits of PCI using drug-eluting stents were

similar.[70] However, in European registries, less women than men are treated with percutaneous or surgical revascularization, clopidogrel and GP IIb/IIIa inhibitors.[64,71,72]

More adverse events with GP IIb/IIIa inhibitors have been reported in women. Indeed, women experience more bleeding than men independently of the type of treatment.[73] Appropriate dosing of antithrombotic agents should improve care of women with NSTE-ACS.

The 2007 ESC Guidelines on NSTE-ACS[74] recommend that women be evaluated and treated similarly to men. The 2008 Guidelines on acute myocardial infarction[75] did not include specific gender-related recommendations.

Gender differences in heart failure

Since 2006, the 11 randomized trials on heart failure[76–86] enrolled 46 141 patients and 12 834 were women (27.8%, range 15–60%) (*Figures 1* and *2*). The mean age was 69.2 years (*Figure 3*) and the mean follow-up was 2.4 years. The majority of trials (8/11; 72.7%) reported the analysis of the results by gender and showed that the effects of main interventions were similar in men and women. The MADIT-CRT trial demonstrated that the benefit of cardiac resynchronization therapy combined with implantable cardioverter-defibrillator (ICD) in relatively asymptomatic patients with a low ejection fraction and wide QRS was significantly greater in women than in men.[87]

An analysis of randomized trials[88] and of the CHARM programme,[78] which enrolled also heart failure patients with a normal ejection fraction—more frequent in women (50%) than in men (35%)—showed that women were older, less often smoked or had prior myocardial infarctions, had higher systolic blood pressures, more diabetes, and more severe symptoms than men. However, women had better outcomes than men. Also the EuroHeart Survey on heart failure, which reflects the clinical practice in Europe,[89] confirmed these findings but, at variance with the randomized trials, 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 as fewer women had an investigation of left ventricular function and were treated with ACE-inhibitors and beta-blockers. Furthermore, an observational study reported that among potentially eligible patients, less women than men received ICD therapy.[90] Thus, women with heart failure in Europe are less often investigated and treated with evidence-based interventions, even after adjustment for age and clinical characteristics.

The 2008 ESC Guidelines on heart failure[91] do not include specific gender-related issues. They state that pregnancy may lead to deterioration of heart failure due to the increase in blood volume and extravascular fluid.

Gender and atrial fibrillation

Overall, the seven randomized trials on atrial fibrillation[92–98] enrolled 28 790 patients and 10 618 were women (36.9%, range 23.3–56.6%) (*Figures 1* and *2*). The mean age was 69.0 years, the mean follow-up was 2.3 years, and three of the seven trials (42.8%) reported the analysis of the results by gender. No gender differences in the outcomes have been observed.

The EuroHeart Survey on atrial fibrillation[99] in 5333 patients (42% female) showed that compared with men, women were older, had a lower quality of life, more co-morbidities, and more often heart failure with preserved left ventricular function. Furthermore, women showed a higher prevalence of additional risk factors for stroke, as indicated by higher $CHADS_2$ scores.[100] One-year outcome was similar, except that women had a higher risk for stroke, independently of age and other risk factors, and are more prone than men to drug-induced proarrhythmia and anticoagulant-related bleeding.[101]

The 2006 ESC Guidelines on atrial fibrillation[102] define female gender as an additional risk factor for stroke, frequent recurrence of paroxysmal atrial fibrillation, and drug-induced ventricular arrhythmias.

Gender differences in stroke

Overall, the 10 randomized trials on stroke[103–113] enrolled 28 790 patients and 10 618 were women (36.9%, range 25–52%) (*Figures 1* and *2*). The mean age of participants was 69.0 years (*Figure 3*) and the mean follow-up was 1.26 years, as the majority of trials have been performed in the acute phase. Five of the 10 trials (50%) reported the analysis of the results by gender.

Gender differences in the clinical presentation and outcome of stroke have been demonstrated. Women have a higher risk of stroke, are more disabled after stroke, and are more likely to be institutionalized.[114] However, women less frequently undergo brain imaging, Doppler examination, echocardiogram, and angiography[3] and less women receive lipid-lowering drugs and antithrombotics for secondary prevention.[115]

Although a meta-analysis showed that women benefit more than men from thrombolysis in acute stroke, less women than men receive this therapy,[3] partly because less women than men reach the hospital within 3–4.5 h and, independently of the delay of arrival, have longer door-to-doctor and door-to-image intervals in the emergency rooms.[116]

The 2008 ESO Guidelines on ischaemic stroke[46] recommend the same management and treatment for women and men.

Conclusions

The EuroHeart project has shown that despite an increase in the proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischaemic heart disease, and heart failure.

Overall, the 62 randomized trials published since 2006 and analysed here (*Table 1*) enrolled 380 891 participants and 127 716 were women (33.5%) (*Figures 1* and *2*). The mean age of participants was 66.3 years (*Figure 3*) and the mean follow-up was 2.7 years. The percentage of women enrolled in each trial ranges between 15 and 60%, but only 31 of the 62 trials (50%) reported the analysis of the results by gender.

The duration of follow-up may have influenced the number of events in women when compared with those occurring in men,

Table 1 Clinical trials

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 (60.0)
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	7181	28.9	65.3	3.4	2/3 (66.7)
Ischaemic heart disease	90 400	24 756	27.3	62.6	1.0	5/13 (38.4)
Heart failure	46 141	12 834	27.8	69.2	2.4	8/11 (72.7)
Atrial fibrillation	22 511	9192	40.8	72.1	2.5	3/7 (42.8)
Stroke	28 790	10 618	36.9	69.0	1.3	5/10 (50.0)
Total	380 891	127 716	33.5	66.3	2.7	31/62 (50.0)

as females of the same age of 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-effectiveness trial execution may be overcome by a more accurate choice of the inclusion criteria. A positive example comes from the JUPITER trial of primary prevention with statins, where men older than 50 years and women older than 60 years have been enrolled.[37] Of note, the age of participants in the majority of the other clinical trials is not reported by gender.

The under-representation of females in cardiovascular research may be partly explained by a lower willingness of women to be enrolled, due to their misperception of risk of cardiovascular disease and/or the difficulties in terms of transportation or support for the follow-up visits. Any barrier to the enrolment of women in clinical trials should therefore be removed.

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

However, more adverse effects for some drugs and procedures have been observed in women than in men. Diabetic women treated with thiazolidinediones experienced an excess of fractures, at variance with men, and women treated for ACS were 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 ACS which deserves the design of studies with a large representation of women.

Cardiovascular clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis should be conducted. Enrolment criteria and follow-up duration should allow the inclusion of women at risk of developing cardiac events. Scientific research on gender issues in cardiovascular medicine should be promoted.

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Appendix

Members of the Advisory Board of the European Heart Health Strategy EuroHeart Project, Work Package 6 'Women and Cardiovascular Diseases': Harisios Boudoulas (Hellenic Cardiac Society, Greece); Emanuela Folco (Italian Heart Foundation, Italy); Marleen Kestens (European Heart Network); Susanne Logstrup (European Heart Network); Peggy Maguire (European Institute of Women's Health, Ireland); Ruairi O'Connor (British Heart Foundation; United Kingdom); Sophie O'Kelly (ESC); Karin Schenck-Gustafsson (Karolinska University Hospital, Sweden); Hans Stam (European Heart Network); M.S.-B. (IRCCS Istituto Auxologico Italiano, Italy); Saila Vikman (Finnish Cardiac Society, Finland).

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