

One more look at guidelines for primary and secondary prevention of cardiovascular disease in women

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Abstract

The most common cause of death in menopausal women is due to complications from cardiovascular disease. However, many physicians feel that the prevention in women may be delayed, because women present the clinical manifestations of cardiovascular disease 10 years later than men. Another matter emerged following the results of the Women's Health Initiative study and of the Heart Estrogen/Progestin Replacement Study. Thus the proper interpretation and implementation of science should be included in a strict procedure of appreciation and clear communication for both the qualitative and quantitative evaluation of evidence, used for the clinical guidelines. Based on objective scientific collaboration among various specialities, guidelines for the prevention of cardiovascular disease of adult women with a broad range of cardiovascular risk have been formed. In this review, the guidelines or recommendations which have been reported in the last 2 decades by various scientific societies for prevention of cardiovascular disease in women will be analysed.

Key words: women, coronary artery disease, premenopausal, postmenopausal, hormone replacement therapy.

Introduction

The most common cause of death in menopausal women is due to complications from cardiovascular (CV) disease and the most severe complication of CV disease is sudden death. In the Framingham Heart Study [1-4], it was found that 2/3 of women who died suddenly had been asymptomatic before. No wonder that these circumstances lead medical societies to suggest more intensive primary and secondary prevention in women [5]. However, many physicians feel that the prevention in women can be delayed, because women present the clinical manifestations of CV disease 10 years later than men. Another matter emerged following the results of the Women's Health Initiative study [6, 7] and of the Heart Estrogen/Progestin Replacement Study (HERS) [7]. Both studies unexpectedly reported an association between combined hormone replacement therapy (HRT) and increased CV events [8-11]. This required a critical review and strategy based on documented evidence for prevention of CV disease in women. The proper interpretation and implementation of science with the aim of improving preventive care should be included in a strict procedure of appreciation and clear communication for both the qualitative and quantitative evaluation of evidence used for the clinical guidelines. Moreover, all existing evidence, including that for men, should be involved after modification for the

formulation of the guidelines for women. Additionally, many patients do not share a similar clinical profile to patients participating in clinical trials; thus the conclusions should be drawn regarding the potential similarities, and generalization from basic research to clinical practice.

Based on objective scientific collaboration among various specialities, guidelines for prevention of CV disease of adult women with a broad range of CV risk have been formed.

Also, after 2 decades of applying the most sophisticated techniques for the diagnosis of CV disease in its early stages, the classification as primary and secondary prevention has become less important. Instead, the grading of CV risk and identification of a high risk group have become more significant.

The guidelines do not represent obligatory rules, but aim at updating physicians' knowledge regarding the severe problem that every aging woman is going to face, and its prompt implementation. Below, the guidelines or suggestions which have been reported in the last 2 decades by various scientific societies for prevention of CV disease in women will be analysed.

American Heart Association Scientific Statement 'Cardiovascular Disease in Women'

In 1997 the American Heart Association (AHA) published 'Cardiovascular Disease in Women' [5]. In this statement the role of major risk factors (RFs), preceding CV disease, such as smoking, arterial hypertension (including isolated systolic hypertension), dyslipidaemia, diabetes mellitus, obesity, sedentary life style, and unhealthy diet, has been emphasized [5]. Smoking was considered to be the first reversible RF and responsible for > 50% of myocardial infarctions (MI) in middle aged women [12]. Moreover, it was emphasised that CV RFs which are manifested in women have different frequency and their reduction is often less intense than in men. For example, the rate of reduction of smoking is lower in women than in men. The incidence of obesity increases more often in aging women than in aging men. Also, more than 52% of women aged above 45 years old present an elevated blood pressure, and more than 40% of women aged above 55 years old present elevated blood cholesterol levels [5].

However, as far as primary prevention is concerned, pharmacotherapy has been recommended only for the high risk group of patients, and a change of lifestyle, such as cessation of smoking, regular physical activity, maintenance of a normal body weight, and consumption of a diet containing low unsaturated fatty acids and intake of increased amounts of fruits and vegetables, has been stressed.

Concerning secondary prevention after MI, physicians should consult the guidelines, published in 1995 and 1996, for the management of patients with acute MI [13-16]. According to these guidelines the administration of β -blockers, inhibitors of

angiotensin-converting enzyme (ACE) (when the left ventricular ejection fraction is < 40%), aspirin and lipid-lowering drugs was recommended. The administration of calcium channel blockers, antiarrhythmic drugs, or magnesium, has not been recommended as a routine therapy during the occurrence of an MI or later.

Concerning secondary prevention after stroke, the guidelines have recommended only the administration of aspirin. Moreover, according to this statement, the administration of HRT in postmenopausal women has been recommended on an individualized basis.

AHA/ACC Scientific Statement: Consensus Panel Statement

The first guidelines regarding the prevention of cardiac disease in women were published in 1999 by the American Heart Association (AHA)/American College of Cardiology (ACC) Scientific Statement: Consensus Panel Statement [17, 18]. Until then, the medical community had not paid great attention to RFs in women. In the HERS study [7], only 10% of participating women presented desirable low density lipoprotein (LDL) cholesterol levels, according to the guidelines of the National Cholesterol Education Program (NCEP) [19, 20]. Moreover, women had fewer possibilities to participate in a rehabilitation programme, after an MI, leading to less intensive treatment. However, in 1995 and 1997, the recommendations for primary and secondary prevention of coronary heart disease, which could be applied to women, were published (see above).

There is an exceptional aspect of women's RFs. This advantage of women had not been mentioned before in any guidelines. Pregnancy and the life period before pregnancy represent the most favourable period of a woman's life for reviewing the RFs and lifestyle, in order to limit the future CV morbidity. The cessation of smoking in pregnant women should be recommended to be continued also after the delivery. The prevention of excess increase of body weight during pregnancy may reduce the risk of occurrence of future events of CV disease. The prevention in women should be emphasized since it is essential, having in mind that CV disease in women increases with age.

In those guidelines, the administration of HRT in perimenopausal and postmenopausal women for the prevention of CV disease, osteoporosis, or possible dementia was also a decision that physicians should make. In particular, physicians should consider the potential favourable effects of HRT and underlying complications of these drugs, including breast cancer, uterus cancer, thromboembolic episodes and diseases of the gallbladder.

Furthermore, the guidelines emphasized that the regulation of RFs preceding CV disease, such as diabetes mellitus and other RFs (abnormal lipid profile

and/or arterial hypertension), plays an essential role in reducing CV events. For example, low plasma high density lipoprotein (HDL) cholesterol level in women aged > 65 years is considered to be more important for the prediction of CV disease than in men at the same age [21]. At that time, the guidelines of the NCEP (ATP II, 1994) [22] stressed the imperative need for more aggressive management of low HDL cholesterol and elevated triglyceride levels in women. In the same guidelines, a recommendation for administration of HRT to postmenopausal women for the regulation of increased LDL cholesterol was introduced [22]. If LDL cholesterol levels remained elevated, a recommendation for administration of a lipid-lowering drug, and in particular statin (inhibitors of HMG CoA reductase), was introduced. Nowadays, this recommendation has been modified (see below), and administration of statins in postmenopausal women represents a first line choice, with the same favourable results as in men.

Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women

In 2004, the guidelines (Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women) were published by the Experts Committee, with Mosca being the first author [23, 24]. A great effort has been made in order to create evidence-based guidelines. In these guidelines, women were classified in groups, depending on risk level (high, moderate, low, and favourable). As a high risk group (Framingham global risk (10-year CV risk) > 20%) were classified women who have been diagnosed with coronary heart disease, stroke, peripheral artery disease, abdominal aortic aneurysm, diabetes mellitus or chronic renal failure. As a moderate risk group (Framingham global risk 10-20%) were classified women with subclinical CV disease (coronary artery calcification) or metabolic syndrome or multiple RFs or one significantly elevated RF, or who have 1st degree relatives with early CV disease (< 55 years in men and < 65 years in women). As a low risk group (Framingham global risk < 10%) were classified women who have only one or no RF, while women with optimal levels of RFs and heart healthy lifestyle should be characterised as a favourable risk group (Framingham global risk < 10%).

Also, it should be noted that the Expert Committee has classified for the first time the clinical recommendations, depending on evidence. Evidence was classified (Table I) according to the type of study and its primary endpoints (death, MI, stroke, revascularization procedures (angioplasty or aortocoronary bypass) and heart failure or some combination of them). Finally, the Expert Committee formulated the clinical guidelines for women (Tables II and III) [23, 24].

The diet recommended by the Experts Committee concerned healthy nutrition. The Experts Committee has concluded that the consumption of fish is correlated with the reduction of risk for CV disease. However, women of reproductive age, and particularly pregnant women, should avoid the consumption of fish such as shark, swordfish, chub mackerel, common mackerel, and finally, white cod, because those fish contain high amounts of mercury, and may affect the normal growth of the nervous system of the fetus. Pregnant women are allowed to consume fish such as salmon and sole.

For the management of classical RFs, the Experts Committee has referred physicians to the guidelines of Scientific Associations, respectively the National Cholesterol Education Program Adult Treatment Panel III [19], the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [25], and the American Diabetes Association [26].

Concerning the treatment of high blood pressure, in hypertensive patients, women and men, lowering blood pressure causes a significant reduction of CV events. Treatment with thiazide diuretics is recommended as a first line therapy while β -blockers are not prescribed now as a common antihypertensive therapy in patients with no complications [25].

Table I. Classification of evidence levels [23, 24]

Classification	Strength of recommendation
Class	
I	Intervention is useful and effective
Ila	Evidence is in favour of usefulness and efficacy
Ilb	Usefulness and efficacy are less established
III	Intervention is not useful and may be harmful
Level of evidence	
A	Adequate confirmation from multicentre, randomised trials
B	Limited evidence derived from a single randomised, or non-randomised trial
C	Based on opinions of experts, case reports, or implemented care
Generalizability index	
1	Great probability for the results to be extended also to women
2	It is possible that results can be extended also to women
3	It is unlikely the results can be extended also to women
0	The extension to women cannot be confirmed

Table II. Clinical recommendations, for lifestyle and major RFs intervention, in women [23, 24]

Clinical recommendations	Class, level, generalizability index
Lifestyle interventions	
Cigarette smoking: consistently encourage women to avoid smoking, active or passive	I, B, 1
Physical activity: consistently encourage women to perform exercise of moderate intensity, for 30 min (brisk walking), on most days of the week, preferably on all days of the week	I, B, 1
Cardiac rehabilitation: women, after an acute coronary event, or an intervention in coronary arteries, or with chronic angina pectoris, should participate in a comprehensive risk reduction regimen such as cardiac rehabilitation programme, or should implement the instructions of the physician at home, or should participate in a community programme	I, B, 2
Heart healthy diet: constant encouragement to follow a healthy diet, e.g. consumption of a variety of fruits, vegetables, cereals, dairy products with low or without fat, consumption of fish, legumes, and proteins with low content of unsaturated fat (poultry, lean meat, plant). Restriction of consumption of unsaturated fat (< 10% of total calories), cholesterol (300 mg/daily), and trans-fatty acids	I, B, 1
Weight maintenance or reduction: constant encouragement of maintenance of body weight or reduction, a proper balance between physical activity and caloric uptake, and, if necessary, implementation of a regular programme, for a body weight index of 18.5 kg/m ² to 24.9 kg/m ² and a waist circumference < 88 cm to be maintained/accomplished	I, B, 1
Psychosocial factors: women with CV disease should be evaluated for potential depression, and should be reported or cured when there are indications	Ila, B, 2
Ω-3 fatty acids: these substances may be administered in high risk women, in the form of diet supplements	Ilb, B, 2
Folic acid: it may be administered in high risk women, as a diet supplement, if homocysteine levels are high	Ilb, B, 2
Major RF intervention	
Arterial hypertension – lifestyle: encouragement to maintain a favourable blood pressure level of < 120/80 mmHg, during all lifetime	I, B, 1
Arterial pressure – drugs: pharmacotherapy is indicated when arterial pressure is > 140/90 mmHg, or lower, in combination with damage of target organ, influenced by hypertension. Thiazide diuretics should be one of the drugs if there are no contraindications	I, A, 1
Lipids, lipoproteins: women's favourable levels are < 100 mg/dl for LDL cholesterol, > 50 mg/dl for HDL cholesterol, < 150 mg/dl for triglycerides, and < 130 mg/dl for non-HDL cholesterol (total cholesterol – HDL cholesterol). Lifestyle change should be encouraged	I, B, 1
Lipids – dietary therapy: consumption of saturated fat should be reduced to < 7% of total calories, and cholesterol to 200 mg daily, in high risk women, or with elevated plasma LDL cholesterol levels. Consumption of trans-fat should also be reduced	I, B, 1
Lipids – pharmacotherapy – high risk: initiation of LDL lowering treatment (statins preferred), along with lifestyle change, in high risk women, and LDL cholesterol ≥ 100 mg/dl.	I, A, 1
Initiation of treatment with statins for LDL lowering in high-risk women, and LDL cholesterol < 100 mg/dl, unless contraindicated. Initiation of treatment with nicotinic acid or fibrates when HDL cholesterol is low or non-HDL cholesterol is elevated	I, B, 1
Lipids – pharmacotherapy – moderate risk: Initiation of LDL lowering treatment (statins preferred), along with lifestyle change, when LDL cholesterol is ≥ 130 mg/dl. Nicotinic acid or fibrates when HDL cholesterol is low, or non-HDL cholesterol is high, after the target LDL cholesterol level has been accomplished	I, A, 1 I, B, 1
Lipids – pharmacotherapy – low risk: initiation of LDL lowering treatment in women with 0-1 RFs and LDL cholesterol ≥ 190 mg/dl, or multiple RFs and LDL cholesterol ≥ 160 mg/dl. Nicotinic acid or fibrates when HDL cholesterol is low, or non-HDL cholesterol is high, after the target LDL cholesterol level has been accomplished	Ila, B Ila, B, 1
Diabetes mellitus: lifestyle change and pharmacotherapy for HbA _{1c} level (haemoglobin adult 1c) < 7% to be accomplished	I, B, 1

Table III. Clinical recommendations for drug interventions, in women [23, 24]

Recommendations	Class, level, generalizability index
Aspirin – high risk: administration of aspirin (75-162 mg daily) or clopidogrel, if there is a contraindication for aspirin, in high-risk women, unless contraindicated	I, A, 1
Aspirin-moderate risk: administration of aspirin (75-162 mg daily) in moderate risk women, provided that blood pressure has been adequately controlled, and its favourable effect exceeds the probability of bleeding from the gastrointestinal system	Ila, B, 2
β-Blockers: these drugs should be administered indefinitely in all women with a history of myocardial infarction, or with chronic myocardial ischaemia, unless contraindicated	I, A, 1
ACE inhibitors: these drugs should be administered in high risk women, unless contraindicated	I, A, 1
Angiotensin II receptor (AT ₁) inhibitors: these drugs should be administered in high risk women with clinically confirmed heart failure, or an ejection fraction of < 40%, who cannot tolerate ACE inhibitors	I, B, 1

In addition, the Experts Committee has formed guidelines for the prevention of stroke in women who developed chronic or paroxysmal atrial fibrillation (Table IV).

The Experts Committee has also established the priority in prevention of CV disease in women, depending on risk group classification. In the high risk group (risk < 20%), the following have been proposed as class I recommendations: smoking cessation, physical activity or cardiac rehabilitation, dietary treatment, maintenance or reduction of body weight when necessary, arterial pressure control, lipid control or statin therapy, aspirin therapy, β-blocker therapy, ACE inhibitor therapy (AT₁ inhibitors when ACE inhibitors are contraindicated) and diabetes control. Also recommended in the same group are the evaluation or treatment of depression and the administration of Ω-3 fatty acids and folic acid as class Ila and class IIb respectively. A class I recommendation dictates that the moderate risk women group (risk 10-20%) should stop smoking, should be familiar with physical activity or cardiac rehabilitation, and maintain body weight or reduce it when necessary. In addition, the same group should be encouraged to follow dietary treatment and treatment of every RF according to the guidelines, whereas according to the class Ila recommendation, these women are advised to follow an aspirin therapy regimen. Moreover, in the low risk group (risk < 10%), smoking cessation, physical activity or cardiac rehabilitation, dietary treatment, maintenance or reduction of body weight and the

proper regulation of every RF for heart disease are rated as class I recommendations. Finally, concerning stroke prevention in women with atrial fibrillation, in the high or moderate risk group it was recommended to receive treatment with coumarin, whereas the low risk group (< 1%) or women with contraindications for administration of coumarin regimen should be treated with aspirin according to a class I recommendation.

For the first time these guidelines clarified if patients should be prescribed HRT. Based on recent studies, HRT has been recommended as class III, level A. This conservative management of postmenopausal women is recommended, until new data from clinical studies would emerge. The Experts Committee concluded that administration of hormone replacement for the amelioration of symptoms or for osteoporosis concerns other scientific organizations.

Recommendations from the U.S. Preventive Services Task Force (USPSTF)

In 2005 the recommendations from the U.S. Preventive Services Task Force (USPSTF) were published [27]. The USPSTF categorized its recommendations according to one of five classifications depending on level of evidence. If the USPSTF strongly recommends physicians to provide the recommendations to eligible patients and has found enough evidence, proving the benefits, then this recommendation is classified as class A. When the USPSTF

Table IV. Prevention of stroke in women with atrial fibrillation [23, 24]

Guidelines	Class, level, generalizability index
Coumarin – atrial fibrillation: in women with chronic or paroxysmal atrial fibrillation, coumarin should be administered, for INR to be maintained at a level of 2.0-3.0, unless the risk for a stroke is < 1%, or there is a high risk of bleeding	I, A, 1
Aspirin – atrial fibrillation: in women with chronic or paroxysmal atrial fibrillation, aspirin can be administered, in a dose of 325 mg/daily, if there is a contraindication for administration of coumarin, or the risk of a stroke is < 1%	I, A, 1

recommends physicians to provide the recommendations to eligible patients and has found enough evidence, proving that benefits exceed complications, the recommendation is categorised as class B. The class C recommendation means that the USPSTF has found evidence proving that the benefits just counterbalance the complications and makes no recommendation for or against the implementation of guidelines, while when the USPSTF recommends against routine implementation of guidelines and has found enough evidence proving that it is not effective and the complications exceed the benefits, the recommendation should be characterized as class D. Finally, the class E recommendation shows that the USPSTF does not recommend the implementation of guidelines, because there is no evidence concerning either benefits or complications. In these guidelines the main points regarded the administration of HRT in postmenopausal women [27]. The USPSTF concluded that administration of a combination consisting of oestrogens and progesterone for management of chronic diseases in postmenopausal women should not be advised in everyday practice, as also was stated in Evidence Based Guidelines for Cardiovascular Disease Prevention in Women. The administration of HRT has been classified as Class D. The USPSTF has found quite enough evidence proving that HRT has not been effective, and potential complications exceed the possible benefits.

The combination of oestrogens with progesterone has beneficial effects on reduction of fractures [28] and intestine cancers [29, 30], but has no effect, or even increases, the CV, thromboembolic [31, 32] and cholecystitis events [8, 33], elevates the risk of occurrence of breast cancer [34-37], strokes [38] and dementia [39], and finally reduces cognitive functions [40]. The USPSTF has reported that postmenopausal women present a possibility of having coronary heart disease (46%), stroke (20%), hip fractures (15%), breast cancer (10%), and uterus cancer (2.6%) [27].

Cardiovascular Diseases in Women: a Statement from the Policy Conference of the European Society of Cardiology

The European Society of Cardiology in 2006 initiated the extensive programme "Women at Heart", aiming to coordinate the research and further education for the prevention of CV disease in women and particularly of coronary heart disease and strokes [41]. The first stage of this programme was to establish a regular conference for recording various issues. A lot of topics have been discussed, and some of them will be analysed below.

In 2004, the World Health Organization published an estimation that in Europe, CV disease is responsible for 43% of deaths in men and 55% in women [41]. Coronary heart disease is responsible for 21% of deaths in men and for 23% in women, while stroke is responsible for 11% of deaths in men and

18% in women. However, women have not realized this risk [23] and still believe that breast cancer causes more deaths.

Another topic which has been discussed at this conference concerns the difference in response to therapy between the two genders. For example, aspirin administration reduces mortality from stroke, and yet does not affect the mortality caused by MI (in contrast to what happens in men) [42].

During this conference the tables evaluating the probability of death in the next 10 years (SCOPE charts) were created. Also, HRT in postmenopausal women (not recommended for the prevention of CV disease), the difference that exists concerning the manifestation and management of coronary heart disease between the two genders, the risk and therapy of stroke in women with atrial fibrillation, and finally the cost-benefit ratio, were analysed [41].

Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women (Updated)

In 2007, the updated clinical guidelines for the prevention of CV disease in women were published (Tables V and VI) [43, 44]. Below, only the differences between the previous guidelines will be analysed.

The classification of women, depending on risk level, has been partially modified in comparison with the Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women. Women with documented coronary heart disease, stroke, peripheral artery disease, abdominal aortic aneurysm, end stage renal disease, diabetes mellitus or Framingham 10-year global risk > 20% are classified as a high risk group. In addition, women with one or more than one major RF for CV disease, such as smoking, unhealthy diet, physical inactivity, obesity and specifically central obesity, arterial hypertension, metabolic syndrome, dyslipidaemia and family history with an early CV disease (< 55 years in men, and < 65 years in women) are categorized in the moderate risk group. Also, women who present reduced tolerance in exercise stress testing and/or abnormal heart rate after the test or evidence of subclinical CV disease according to coronary artery calcification belong to the moderate risk group. Finally, women who have a healthy lifestyle, no RF or Framingham 10-year global risk > 20% should be classified in the favourable risk group.

Emphasis has been paid to the total risk (of the whole lifetime) and not only to the next 10 years, which is determined by the Framingham algorithm.

Aspirin administration for the prevention of CV disease in women aged > 65 years, or for the prevention of stroke in women aged < 65 years, is cited in Table V.

Conclusions

The CV diseases, in spite of the significant interventions that have been made for primary and

Table V. Clinical guidelines for women [43, 44]

Management	Class, level
Aspirin – high risk Administration of aspirin (75-365 mg) if no contraindications When there is intolerance to aspirin in high risk women, clopidogrel would be administered	I, A I, B
Aspirin – other risks or healthy women In women aged ≥ 65 years, aspirin administration (81 or 100 mg every other day), provided there is adequate control of arterial pressure, and as long as the favourable effects on prevention of MI or stroke exceed the potential of a haemorrhage from the gastrointestinal system and cerebral arteries	IIb, B
β -Blockers β -Blockers should be indefinitely administered in all women with a history of MI, or with myocardial dysfunction, with or without symptoms of cardiac failure, if there are no contraindications	I, A
ACE inhibitors/AT ₁ inhibitors The ACE inhibitors should be administered if there are no contraindications, in women with an MI and clinical manifestations of heart failure, or with an ejection fraction $\leq 40\%$, or with diabetes mellitus In women with MI and clinical manifestations of heart failure, or with an ejection fraction $\leq 40\%$, or with diabetes mellitus and intolerance to ACE inhibitors, angiotensin II, AT ₁ receptors antagonists should be administered	I, A I, B
Aldosterone antagonists These drugs should be administered after an MI, provided there is no severe renal insufficiency, or hyperkalaemia, and if ACE inhibitors, β -blockers are received, an ejection fraction $\leq 40\%$, and symptoms of heart failure are presented	I, B

Table VI. Management of class III for the prevention of CV disease and MI in women [43, 44]

Management	Class, level
Treatment of menopause The HRT for selective control of ER receptors (SERMs) should not be administered for either primary or secondary prevention of CV disease	III, A
Antioxidative supplements Antioxidative vitamin supplements (vitamin E, C, β -carotene) should not be administered for primary or secondary prevention of CV disease	III, A
Folic acid Folic acid, with or without supplements of vitamins B ₆ or B ₁₂ , should not be administered for primary or secondary prevention of CV disease	III, A
Aspirin for the prevention of MI in women aged < 65 years Daily administration of aspirin in women aged < 65 years old should not be recommended for prevention of myocardial infarction.	III, B

secondary preventions, are still the main cause of death in men and women of the western world [18, 45]. Particularly, concerning women, deaths from CV disease, in every age group, are more prevalent and even higher than breast cancer [46]. Furthermore, in women, when the CV disease is revealed, the prognosis is more threatening compared to men. In the guidelines of the American Heart Association (AHA Scientific Statement, Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women, see above), Mosca *et al.* [23] reported that in the United States of America, more than half a million of women were dying from CV disease each year. The World Health Organization (WHO) reported that women's deaths due to MI or stroke had a linear relationship with age.

The prevalence of MI in women with normal levels of oestrogens is very low (1% to 7% per 100 000) and

3-5 times lower than in men. Some studies suggested genetic variability [47]. However, this favourable relationship disappears in older women (> 65 years). The major determinant differentiating women from men is oestrogens. Oestrogens exert various actions on the organs of the human body, and particularly on the female body [48-51]. Their levels vary during the woman's life time and influence many organs.

The results from the clinical trials, reported by many investigators, regarding the hormone status of women and the occurrence of CV events have led to the conclusions that oestrogens exert a protective effect on atherogenesis, on the formation of atherosclerotic plaque, and subsequently on clinical manifestation of atherogenesis, namely CV disease. During the past years, the management of women has detained several scientific organizations, which have published

guidelines. These guidelines are practical and helpful for physicians for the primary and secondary prevention of CV disease in women of all ages.

Observational studies reported that HRT was effective for most symptoms and diseases (particularly CV and osteoporotic disease) of menopausal women, and its use was recommended. However, disadvantages of HRT emerged from two large randomised controlled trials, HERS [7] and WHI [6], that found no benefits for prevention of CV diseases. Particularly, the WHI trial found an increase in breast cancer incidence and in CV events in healthy women. Later, the Million Women Study [52] showed an increase in breast cancer incidence associated with HRT. The publication of these findings led to different interpretations, among researchers, specialists (mainly gynaecologists and oncologists) and general practitioners, of HRT's benefits. Nowadays the use of HRT is limited to women in the early menopause and suffering from hard-to-bear symptoms. The HRT should be used for the shortest possible period and at the lowest effective doses. However, the results from the Kronos Early Estrogen Prevention Study (KEEPS) [53] and the Early versus Late Intervention Trial with Estradiol (ELITE) [53] are expected. Until then, HRT has been graded as a class III recommendation for the prevention of CV disease in women.

More research is required to evaluate the long-term benefits and side effects of HRT. However, there are a few new beliefs, for example that by starting HRT near menopause, the side effects may be diminished (the majority of studies evaluating the effects of HRT include women roughly 10 years after menopause). Another significant observation was drawn from the Women's Health in the Lund Area Study (3 600 postmenopausal women without HRT and 2 816 postmenopausal treated with HRT or who were under HRT in the past) [54]. In this study, women who were receiving HRT had fewer risk factors for CV disease and followed a healthier lifestyle. Also, transdermal vaginal preparations may reduce certain adverse effects (breast, uterus and bowel cancer, pulmonary embolism) [55]. Additionally, low doses and very low doses of hormones may be more appropriate, especially in older women [56]. Until then, HRT should be decided by the physician separately for each woman based on symptoms, health status, personal beliefs and expectations. The individual risk-benefit balance is very important.

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