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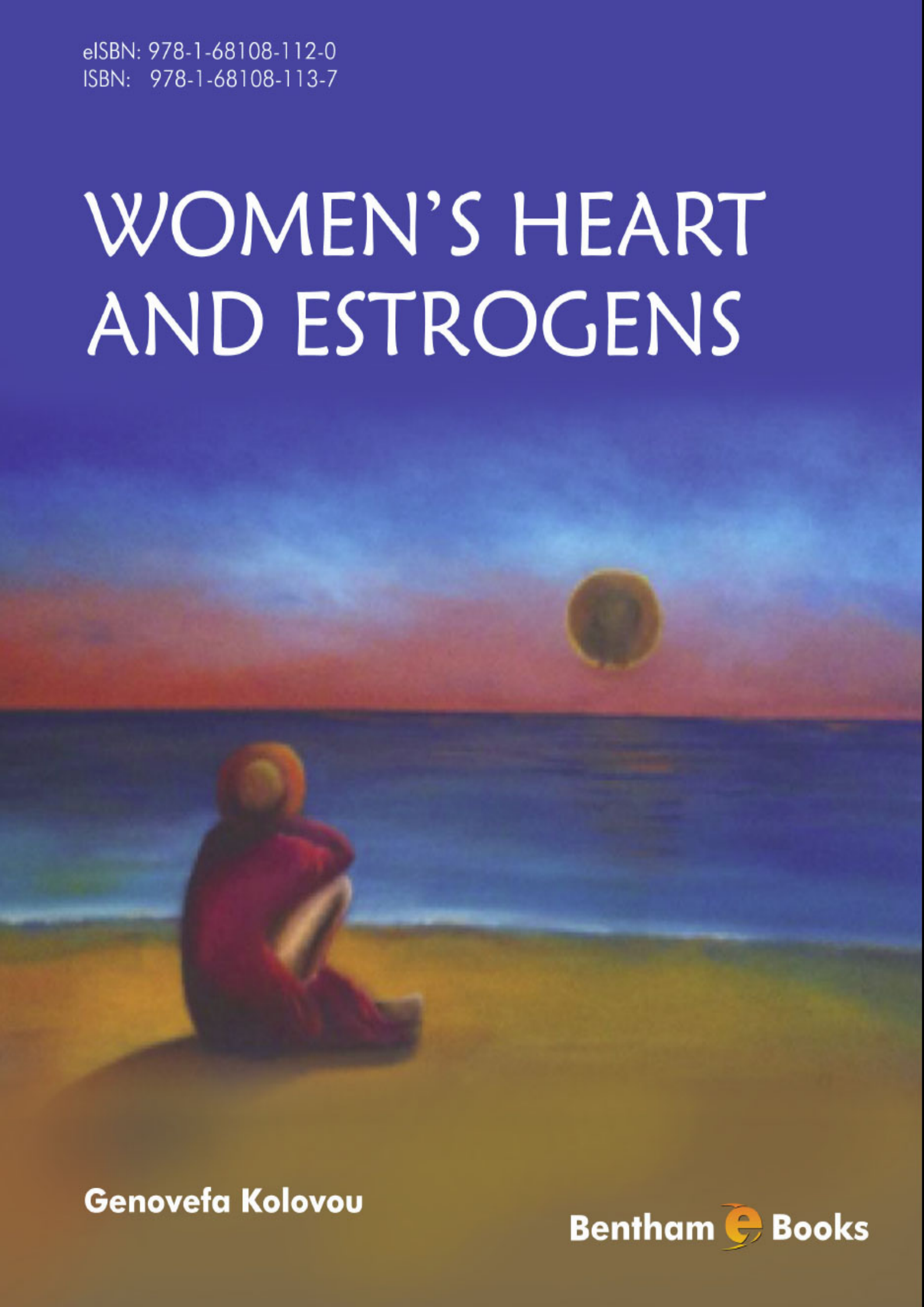
WOMEN'S HEART AND ESTROGENS



Genovefa Kolovou

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WOMEN'S HEART AND ESTROGENS

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FOREWORD

I read Genovefa's book with pleasure although it is dealing with complicated subjects such as women's heart.

The book is generously offering knowledge, which is presented with clarity, simplicity and elegancy. The book initiates with a description of the established and newly proposed metabolic pathways involving estrogen actions and ends with more recent published studies and recommendations.

Genovefa, writing her thirteenths book took care in exhausting every option of the women's heart and lead reader to solve all their queries.

In the first two chapters there has been a referral to a very important issue such as estrogens involvement in cardiovascular system and atherogenesis. Moreover, the classification of causes leading to the development of early onset of coronary heart disease in young women is particularly useful. The differences observed in the lipid profile, obesity, and levels of the blood glucose and blood pressure of peri- or post-menopausal women are described in the 3rd chapter.

Also, the studies involving women treated with hormone replacement therapy and cardiovascular outcomes are summarized nicely in chapter 4. Furthermore, after analyzing the prevention of cardiovascular disease in women, in chapter 5, guidelines according to prevention of cardiovascular disease in women (chapter 6) are also presented. The guidelines are analyzed according to publication date, which allows reader to go through the 15-year development of current guidelines.

Moreover, the significant parts of this important work are played by figures and main points, which summarized each chapter. This allows reader the quick comeback to the chapter. I wish all the best with your new book.

Helen Bilianou
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PREFACE

The prevalence of cardiovascular risk factors as well as the clinical and molecular pathophysiology of cardiovascular disease is different between men and women. Particularly, in that of a variety of pathological conditions, such as premature menopause, gestational diabetes mellitus, pregnancy-induced hypertension and polycystic ovarian syndrome which affect only women. Furthermore, a number of other diseases, such as migraine, Raynaud's phenomenon, vasculitis and coronary artery spasm are more common in women compared with men.

Additionally, postmenopausal and elderly women more frequently present the classical risk factors for cardiovascular disease (dyslipidemia, arterial hypertension, diabetes mellitus, obesity, sedentary lifestyle and others) than men of the same age. What's more, women presented with cardiovascular disease are older and subsequently, commonly manifest accompanying abnormalities such as osteoporosis, compared with men of the same age. The end result of all that is mentioned above is that, women have different mechanisms, contributing to the severity and outcomes of cardiovascular disease.

The most important factor differentiating women from men is estrogen. Estrogen is not a single hormone. The term "estrogen" is really referred to a group of several related hormones (mainly estradiol, estrone and estriol), which perform the functions we normally attribute to "estrogen". Thus, in this handbook for practical reasons the word "estrogen(s)" will be used.

Estrogens exert a variety of actions particularly on the female’s body. Their levels vary during a woman’s lifetime and influence many vital systems. One of the most important systems undergoing remarkable changes after reduction of endogenous estrogens is the cardiovascular. Estrogens may act directly on the blood vessels or through modification of the cardiovascular risk factors, including arterial hypertension, obesity, diabetes mellitus, dyslipidemia, and others. Menopause and ageing are the two main parameters, which lead to unfavorable alterations of the classical risk factors in women.

In this handbook, the mechanisms of estrogen actions on the cardiovascular system and the alterations associated with estrogen production, based on studies of several researching teams, including our own will be discussed. Moreover, the changes in the body composition of postmenopausal women and the manner by which they may contribute to unfavorable modifications of classical risk factors will be also analysed.

Epidemiological and clinical trials, as well as the cardiovascular management of women will be reported.

The management of women's population has been the subject of several scientific societies, which have published several guidelines. These guidelines are not obligatory rules, but aim to inform health providers of the severity of the problem and render them capable to make decisions, concerning the institution, benefits and potential adverse effects of a particular treatment. Some of these guidelines will be also presented.

For all the aforementioned reasons, a review of more than ten thousand titles or abstracts have been completed and approximately three thousand papers have been looked up, out of which approximately 850 are mentioned in this handbook.

Only articles edited in PubMed and in the English language were looked for. We believe that this handbook will provide a condensed and yet complete up-to-date overview of the woman's cardiovascular system during her various life periods, and will facilitate the practicing physician to make important decisions.

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CHAPTER 1

Estrogens and Atherogenesis

Abstract: In the 21st century, cardiovascular disease has become a global cause of morbidity and a main contributor to mortality in most countries, regardless of the important actions which have been endorsed for primary and secondary prevention. Concerning women's cardiovascular mortality, in all age groups it is more frequent and even greater than it is due to breast cancer. In this chapter, the stages of atherogenesis, the factors that induce atherogenesis (environmental and genetic), the effects of estrogens on the stages of atherogenesis, and finally, the effects of estrogens on those components will be analyzed.

Keywords: Apolipoprotein E gene polymorphism, Atherogenesis, Cholesterol, Cholesteryl ester transfer protein gene polymorphism, Estrogens, Estrogen receptor gene polymorphisms, Familial hypercholeste-rolemia, Sitosterolemia.

1. INTRODUCTION

In the 21st century, cardiovascular disease has become a global cause of morbidity and a main contributor to mortality in most countries, regardless of the important actions that have been endorsed for primary and secondary prevention [1, 2]. Concerning women's cardiovascular mortality, in all age groups it is more frequent and even greater than it is due to breast cancer [3].

It is noteworthy to mention that cardiovascular disease in women is treated in a less aggressive approach compared with men. This difference in treatment is multifactorial and much more compound than gender. Nowadays, it is well-known that women are more likely to develop coronary heart disease roughly 10 years later in her life compared with men. Additionally, women are expected to present coexisting chronic conditions such as obesity, diabetes mellitus, osteoporosis, cancers and others. Investigations have also shown that women may not be diagnosed as vigorously as men, and their symptoms differ considerably from those of men who have experienced a heart attack. It is noteworthy to mention that women's participation in the clinical trials concerning cardiovascular disease

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is underrepresented compared with men's participation.

Mosca *et al.* [2] reported that in the United States of America, >500,000 women die each year from cardiovascular disease and the majority of women who die from sudden cardiac death have no prior history of heart disease. Furthermore, the World Health Organization (WHO) reported that women's mortality due to myocardial infarction or stroke had a linear positive correlation with their age.

The prevalence of myocardial infarction in women with normal endogenous estrogen concentration is very low (1-7% per 100,000) and 3-5 times lower than in men. However, this favorable association weakens in older women (>65 years). De Kleijn *et al.* [4] reported that menstruation abnormality, the number of abortions and the age at the onset of menopause are factors related to an increased risk of cardiovascular disease in women. Furthermore, several trials [5 - 7] have shown that premature menopause leads to a higher risk of developing coronary heart disease; this risk is independent from the other classical risk factors such as arterial hypertension, dyslipidemia, obesity and smoking. Van der Schouw *et al.* [8] reported a 2% decrease in cardiovascular mortality that was associated with every year of delay in the onset of menopause in 12,115 postmenopausal women. Jacobsen *et al.* [9] reported that premature menopause was associated with higher total mortality. On the other hand, the number of cardiovascular deaths was reduced by 60% in women whose menopause occurred after the age of 53 years. Furthermore, Hu *et al.* [10] observed that premature menopause was related to an increased risk of coronary heart disease, particularly in women smokers. Additionally, Saltiki *et al.* [11] reported that the severity of coronary heart disease was correlated with the time interval of endogenous estrogen exposure. Additionally, they found that the time period after the onset of menopause and women's age at menopause were aggrevating factors for myocardial infarction, independently of age. De Kleijn *et al.* [12] found similar results. Moreover, they found a 20% reduction in cardiac mortality in women with a more prolonged endogenous estrogen exposure during their lifetime compared with those with shorter endogenous estrogen exposure. Jansen *et al.* [13] observed that the mortality had decreased in women with more than 40 years of endogenous estrogens exposure during their lifetime compared with those with less than 33 years of endogenous estrogens exposure.

Thus, the results from numerous clinical studies with reference to the hormone status of women and the incidence of cardiovascular events have led to the conclusion that estrogens exert a protective effect on atherogenesis, on formation of the atherosclerotic plaque and subsequently, on clinical manifestations of atherosclerosis.

Cardiovascular diseases represent multifactorial conditions and their manifestations in terms of onset (acute, chronic), presentation (with or without myocardial infarction), severity (mild, moderate, severe) and time of appearance (premature or delayed) are affected by environmental and genetic factors, as well as by gender. However, significant improvement has been made in awareness, treatment, and prevention of cardiovascular disease in women since the American Heart Association (AHA) published the first women-specific clinical recommendations for the prevention of cardiovascular disease in 1999 [1]. Furthermore, over the past years after the scientists have developed animal models for studying atherogenesis, significant progress has been made concerning the understanding of evolutionary, biological and cellular events leading to atherogenesis.

In this chapter, the stages of atherogenesis, the factors that induce atherogenesis (environmental and genetic), the effects of estrogens on the stages of atherogenesis, and finally, the effects of estrogens on the factors, which promote atherosclerosis, will be analyzed.

The term "estrogen" is actually referred to a group of several related hormones (mainly estradiol, estrone and estriol), which perform the functions we normally attribute to "estrogen". Thus, in this handbook for practical reasons the word "estrogen(s)" will be used.

2. ATHEROGENESIS

Atherosclerosis has been a human disease for >3 thousand years. It was found in Egyptian mummies (report on the pathological condition of the aorta of King Menephtah) who was the fourth ruler of the Nineteenth Dynasty of Ancient Egypt and ruled Egypt between 1213-1203 BC and revealed the same pathologic features that are observed in current times.

CHAPTER 2

Cardiovascular Actions of Estrogens

Abstract: The actions of estrogens on the cardiovascular system occur either indirectly through the modification of cardiovascular risk factors [reduction of plasma LDL cholesterol, elevation of HDL cholesterol, effect on hemostatic factors (reduction of fibrinogen and inhibitors of fibrinolysis)] or directly mediated by the estrogen receptors (ERs, defined as genomic action of estrogens) or other receptors. In this chapter, the overall actions of estrogens on the cardiovascular system and particularly on the vascular wall, as well as actions of estrogens on many different metabolic pathways affecting the cardiovascular system will be analyzed. The indirect actions of estrogen on the circulatory and hematological system, body composition, lipids and glucose metabolisms will be analyzed. There are several causes leading to the development of early onset of coronary heart disease in young women. These causes can be classified into five categories: 1) Vasculitis and autoimmune diseases, 2) Hypercoagulable states, 3) Non-atherosclerotic coronary heart disease, 4) Myocardial infarction in hallucinogenic drug abusers, and 5) Atherosclerotic coronary heart disease. The causes leading to an early onset of coronary heart disease in young women will be analyzed.

Keywords: Anti-inflammatory, Anti-proliferative, Autoimmune diseases, Coronary heart disease, Diabetes mellitus, Dyslipidemia, Estrogens, Genomic, Hypertension, Metabolic syndrome, Non-genomic, Vascular endothelium, Vasculitis, Vasodilation.

1. INTRODUCTION

During the reproductive age of women, the control of estrogens is achieved through positive and negative feedback mechanisms involving the hypothalamus, the hypophysis and the ovaries [206], (Fig. **B1**).

The gonadotropic hypothalamic cells produce the gonadotropin releasing hormone (GnRH), which inducts the release of follicle stimulated hormone (FSH), and luteinizing hormone (LH) [207 - 209]. Then, gonadotropins LH and FSH promote the release of steroid hormones (estradiol and progesterone) from the ovaries. These hormones, by acting on the hypothalamus and hypophysis, directly

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contribute to the release of gonadotropins (negative feedback), (Fig. **B1**).

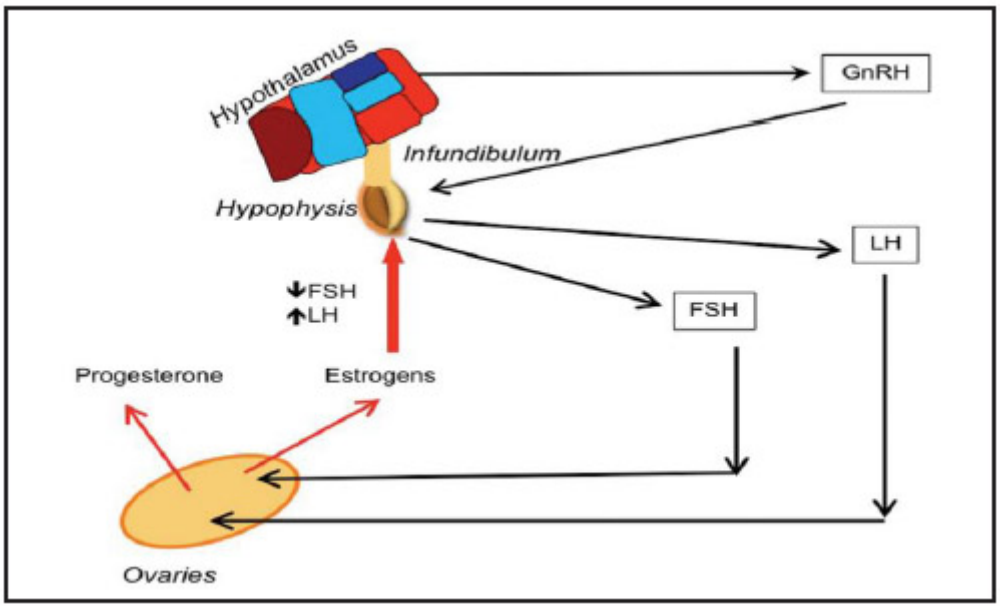

Fig. (B1). Estrogens biosynthesis.
The hypothalamus controls the release of 8 major hormones and is involved in thermoregulation, food and water intake, sexual behavior and reproduction and others. The hypophysis secretes 9 main hormones that control various body functions and the secretory activity of numerous endocrine glands and is divided into the anterior pituitary, or adenohypophysis and the posterior pituitary or neurohypophysis. The follicle stimulating hormone (FSH) stimulates the initial steps and aromatase in granulosa cells from follicies of all size. Luteinizing hormone (LH) stimulates thecal cells after the primary follicile stage and granulosa cells from antral stage follicies. Granulosa cells alone cannot produce estrogens. LH and FSH promote the release of steroid hormones from the ovaries, which, through the hypophysis and the hypothalamus, participate in the control of the release of gonadotropin releasing hormone (GnRH, negative feedback).

The actions of estrogens on the cardiovascular system occur either indirectly through the modification of cardiovascular risk factors reduction of plasma LDL cholesterol, elevation of HDL cholesterol, effect on hemostatic factors (reduction of fibrinogen and inhibitors of fibrinolysis) or directly mediated by the estrogen receptors (ERs, defined as genomic action of estrogens) or other receptors [210].

In a similar way to other steroid hormones, estrogens enter cell membrane passively and bind the ERs. Then, the estrogen/ER complex binds to transcriptional DNAs and modify the expression of genes, (Fig. **B2**). Functional

ERs have been experimentally identified, in both intact and isolated vessels, in cultured endothelial cells and in smooth muscle cells.

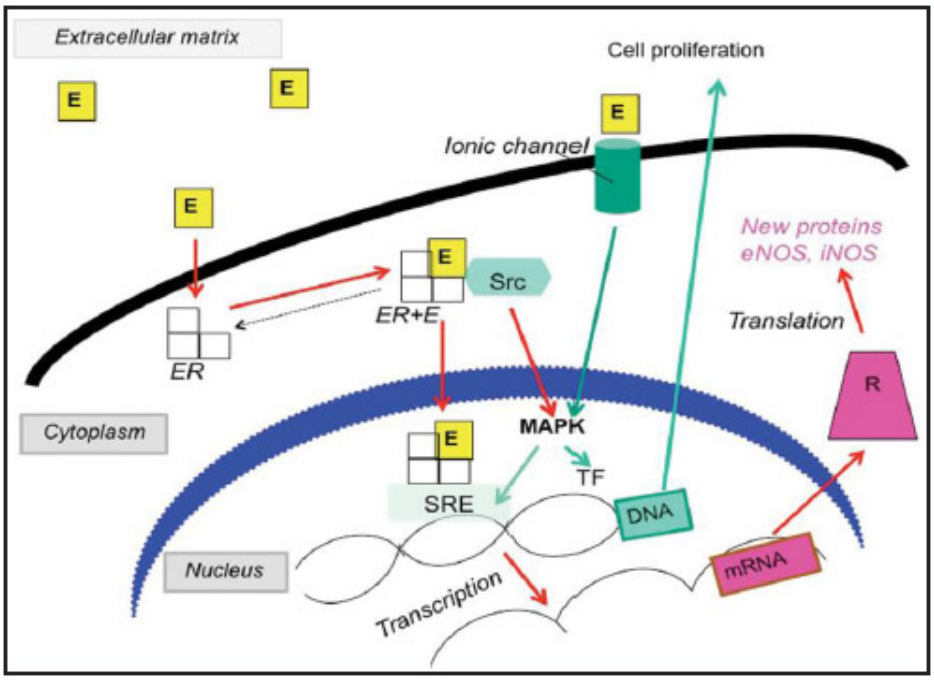

Fig. (B2). Genomic and non-genomic actions of estrogens.
Genomic action of estrogens is depicted by red arrows and non-genomic by other colors. E = estrogen, ER = estrogen receptor, ER+E = estrogen receptor + estrogen, SRE = steroid receptor response element, Src = steroid receptor coactivator, MAPK = mitogen-activated protein kinase, TF = tissue factor, eNOS = endothelial NO synthetase, iNOS = inducible NO synthetase, R = ribosome.

Several mechanisms, related to the actions of estrogens are difficult to be explained by genomic actions, as they occur acutely; they are defined as non-genomic actions [211] of estrogens.

It seems that the actions of estrogens on the vascular wall include both mechanisms (genomic and non-genomic) and can be divided into vasomotor, cellular proliferation and reaction to injury.

In this chapter, the overall actions of estrogens on the cardiovascular system and particularly on the vascular wall, as well as actions of estrogens on many different metabolic pathways affecting the cardiovascular system will be analyzed.

CHAPTER 3

Menopause

Abstract: Natural menopause occurs during the early 50s of a woman's life. The last two decades life expectancy for men and women has risen nationwide. This supports the hypothesis that women may live more than 30 years after the onset of menopause. The decline of estrogens production leads to various, usually annoying, vasomotor symptoms, to other conditions such as obesity, urogenital atrophy, cognition disturbances and eventually to an increased risk for developing degenerative diseases like osteoporosis, cardiovascular and others. The differences observed in the lipid profile of peri- or post-menopausal women are not only due to the decline levels of estradiol and raised levels of estrone, but also due to the changes of body weight. Central obesity, usually observed in peri- and post-menopausal women is associated with elevated plasma triglycerides and low HDL cholesterol concentrations. The organic system, which is affected significantly by menopause, is the cardiovascular one. Alterations in the cardiovascular system due to the rapid decline in endogenous estrogens production will be discussed.

Keywords: Ageing, Blood Glucose, Blood Pressure, Body Composition, Estrogens, Lipid Metabolism, Menopause, Postprandial hypertriglyceridemia.

1. INTRODUCTION

The term menopause is usually referring to the period of a woman's life, which is characterized by the development of various somatic symptoms and complaints [596]. In fact, menopause does not reflect any arbitrary period of time, but instead an important turning point during which, the menstruation ceases signaling the loss of a significant trademark of the female existence, *i.e.* the ability to conceive and have children.

The menstrual abnormalities and menopausal symptoms (Table **C1**) may start at any time, even 2 to 9 years before the onset of menopause. In addition, many of these symptoms will continue to exist for several years after the onset of menopause. This entire period is called climacteric and is classified into 3 phases: premenopausal, perimenopausal and postmenopausal.

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Table C1. The most common menopausal symptoms.

Symptoms
Vasomotor abnormalities: Flushes, perspirations, tachycardia
Sleeping abnormalities: Disruptions in nocturnal sleeping pattern with intermittent perspirations
Psychological abnormalities: Anxiety, depression, over excitation, irritability, reduced libido, reduced ability to perform every day activities
Urogenital abnormalities: Vaginal atrophy, dryness, pruritus, dyspareunia, infections, abnormal frequency of urination, urinary incontinence
Skin and collagen abnormalities: Reduction of elasticity located mainly on the face and neck, dryness and wrinkling, hoarseness, symptoms of masculinization, hirsutism, alopecia
Other symptoms: Chest discomfort, pain and inflammation of joints and/or muscles.

The reduction of estrogens production during the climacteric period may induce numerous uncomfortable symptoms [597], affecting approximately the 75% of women, (Table **C1**). These symptoms usually persist for several years, being sometimes serious enough to significantly deteriorate the women's quality of life.

In the paragraphs below, the main symptoms of menopause will be pointed out and alterations in the cardiovascular system due to the rapid decline in endogenous estrogens production will be discussed [598 - 602].

The World Health Organization Scientific Group on Research on the Menopause [603] has defined menopause as a permanent end of menstruation due to ovarian dysfunction or ovarian surgical removal. It is difficult to calculate, in the objective manner, the exact termination of menstrual cycle. Generally, the process is individualized. Every woman experiences it in a different way.

Natural menopause occurs during the early 50s of a woman's life. The last two decades life expectancy for men and women has risen nationwide. This supports the hypothesis that women may live more than 30 years after the onset of menopause. Demographic studies have predicted that in the following 20 years there will be approximately 1.2 billion of postmenopausal women [604].

The production of estrogens in postmenopausal women is principally extragonadal (adipose tissue, adrenal glands) and the main circulating estrogens

are estrone (50-70% less active than estradiol) and estriol [605]. The hormonal alterations observed after menopause also affects the levels of gonadotropins [mainly the follicle stimulating hormone (FSH) and the luteinizing hormone (LH)]. Similar changes are also observed, as women get older. It has been reported that gonadotropins tend to increase with age due to the action of the gonadotropin releasing hormone (GnRH) produced by the gonadotropic cells of the hypophysis [606]. The FSH concentration remains elevated for many years after the onset of menopause and then declines significantly [607].

The increased concentration of gonadotropins in postmenopausal women affects the function of many cells. Bowen *et al.* [608] reported a significant elevation of LH in the cytoplasm of the pyramidal neurons and neurofibrils in brains with Alzheimer's disease compared with the brains of disease-free women of the same age. In the Study of Women's Health Across the Nation (SWAN, page 130) [609], which included premenopausal and perimenopausal women followed up to 5 years, the rise of the plasma FSH had been more significant related to the bone density determination than the decrease of estrogens [610]. This has been confirmed in the experimental study with transgenic mice (FSHβ or FSH receptor knockout) by Sun *et al.* [611]. They found that neither FSHβ nor FSH receptor null mice have bone loss despite severe hypogonadism and that FSH is required for hypogonadal bone loss. The authors explained that this happened because both prodromal and mature forms of osteoclasts express FSH receptors.

Under normal conditions, FSH after binding to FSH receptor located on the osteoclasts' surface activates the inhibitory G protein that in turn reduces the levels of cAMP and activates MEK/Erk, NF-kB factors and Akt signalling pathways (see page 48). This leads to the differentiation of osteoclasts and the loss of bone mass.

Apart from reduced estrogens production during the menopause transition and/or ageing several other hormones are also affected.

For example, the levels of testosterone [612, 613] and sex hormone-binding globulin (SHBG) [607, 614] decline with advanced age. The others pituitary hormones are usually not affected. In particular, the growth, thyrotropic and

CHAPTER 4

Studies Evaluated Cardiovascular Events in Women Receiving Hormone Replacement Therapy

Abstract: Studies evaluating cardiovascular events solely in women are fewer in comparison with studies evaluating solely in men. Clinical data on the efficacy of antihypertensive, hypolipidemic or antidiabetic treatment are not many. Studies involving women were mainly focused on the influence of hormone replacement therapy on cardiovascular events. Some of these studies were challenged for their design. Many scientists believe that women included in these studies were too old and the period of time after the onset of menopause was too long. In this chapter, studies evaluating cardiovascular outcomes in women receiving hormone replacement therapy will be summarized. Hormone replacement therapy should not be recommended routinely for all postmenopausal women, as it is not clear if it presents cardioprotection and the detectable elevated risk of cardiovascular disease and breast cancer surpasses the benefits in asymptomatic women, by the time the newer data would become available.

Keywords: Ageing, Blood glucose, Blood pressure, Body composition, Estrogens, Lipid metabolism, Menopause, Postprandial hypertriglyceridemia.

1. INTRODUCTION

Studies evaluating cardiovascular events solely in women are fewer in comparison with studies evaluating solely in men. To be more specific, clinical data on the efficacy of antihypertensive, hypolipidemic or antidiabetic treatment are not many; see Chapter 5. PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

Studies involving women were mainly focused on the influence of hormone replacement therapy on cardiovascular events. Some of these studies were challenged for their design. Many scientists believe that women included in these studies were too old and the period of time after the onset of menopause was too long.

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In this chapter, studies evaluating cardiovascular outcomes in women receiving hormone replacement therapy will be summarized. Some studies described in this chapter, are included also in Chapter 5. PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN but from a different point of view. The studies are classified in chronological order by publishing date. The subgroup analyses of the studies are also chronologically referred.

2. STUDIES EVALUATING CARDIOVASCULAR EVENTS IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY

2.1. Heart and Estrogen/Progestin Replacement Study (HERS), 1998

In the HERS study (large, randomized, blinded study of secondary prevention) 2,763 postmenopausal women participated with documented coronary heart disease aged <80 years. Women were treated with 0.625 mg/daily estradiol plus 2.5 mg/daily medroxyprogesterone or placebo. The follow up period was 4.1 years [710].

The primary end points were nonfatal myocardial infarction and cardiac death, while secondary end points included revascularization, nonfatal ventricular tachycardia, sudden death, stroke and peripheral artery disease.

In the first year of the follow up, an increase of cardiovascular events in the treated group compared with untreated group (placebo) was observed. On the contrary, after 2 more years of follow up, a reduction of cardiovascular events in the treated group compared with the untreated group was found.

2.1.1. HERS Study and Peripheral Arterial Disease, 2000

In this study the events from peripheral arteries (carotid, cerebral, arteries of upper and lower extremities, aorta and finally, mesenteric and renal) were evaluated. A total of 311 cases were reported. Treatment with oral conjugated estrogen plus medroxyprogesterone acetate was not correlated with any significant reduction of events from peripheral arteries [711].

2.1.2. HERS Study and Stroke, 2001

In the HERS study 149 strokes (26 fatal) were reported. Hormone therapy with conjugated equine estrogens and progestin had no influence on the risk of stroke [712].

2.1.3. HERS Study and Blood Glucose Levels, 2003

Fasting blood glucose concentrations increased significantly compared with women treated with placebo but did not alter in women treated with hormone replacement therapy, during the 4 year follow up period. Moreover, women under hormone replacement therapy presented a 35% lower risk of the appearance of diabetes mellitus compared with women with no hormone replacement therapy [417].

2.1.4. HERS Study and Uric Acid Levels, 2006

The relationship between hormone replacement therapy and uric acid concentration was examined during the HERS study [713]. Although, hormone replacement therapy produced reduced uric acid levels, this finding was not related to an altered cardiac risk.

2.2. Estrogen Replacement and Atherosclerosis Trial (ERA), 2000

In the ERA trial (randomized, double-blind study of secondary prevention) 235 postmenopausal women with angiographically diagnosed coronary heart disease, aged >55 years, were treated with 0.625 mg/daily estradiol or 0.625 mg/daily estradiol plus 2.5 mg/daily medroxyprogesterone or placebo. Quantitative coronary angiography was carried out at the beginning of the study and after 3.2 years. Study end points included mean minimum coronary artery diameter, the mean percentage of stenosis and the presence of new coronary artery lesions [714].

There was no difference in the primary end points among the treated group and the placebo group. Moreover, no difference in the number of cardiovascular events and deaths was observed.

CHAPTER 5

Prevention of Cardiovascular Disease in Women

Abstract: The increase awareness of cardiovascular risk factors is an important concern and may help to avoid or to moderate an aggressive management of cardiovascular events in the future. The factors (healthy diet, physical activities, body weight reduction and smoking cessation), whose modification could improve the cardiovascular disease outcomes in women, will be analyzed.

Clinical trials that involved women under treatment for dyslipidemia, diabetes mellitus or arterial hypertension will be also analyzed. Moreover, data of hormone replacement therapy in women as well as in animal models will be discussed.

Keywords: Antidiabetic drugs, Antihypertensive drugs, Body weight, Healthy diet, Lipid lowering drugs, Physical activities, Smoking cessation, Women.

1. INTRODUCTION

Lifestyle change has been graded by the Scientific Statement Consensus panel statement "Guide to Preventive Cardiology for Women" [1] as a Class I recommendation. The recommendation was not only for the potential reduction of cardiovascular disease risk, but also because the appropriate lifestyle change may prevent or delay the appearance of the major risk factors for cardiovascular disease [1].

The increase awareness of cardiovascular risk factors is an important concern and may help to avoid or to moderate an aggressive management of cardiovascular events in the future.

The factors, whose modification could improve the cardiovascular disease outcomes in women, will be analyzed below.

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2. HEALTHY DIETS AND CARDIOVASCULAR RISK

The increased uptake of dietary cholesterol and triglycerides results in enhancing their transport from the small intestine to the liver within chylomicrons. This leads to engagement of LDL receptors and elevation of plasma LDL cholesterol concentration. High circulating levels of LDL cholesterol are also caused by the decreased catabolism of LDL and VLDL particle remnants and by the increased rate of transformation of VLDL to LDL particles [754].

Saturated fatty acids contribute significantly to plasma cholesterol and triglyceride concentrations compared with other dietary substances. Saturated fatty acids are derived from animal fat and plant oils. A high intake of saturated fatty acids may increase the levels of the plasma total and HDL cholesterol and triglycerides [754].

Nowadays, it is well established that diet affects the cardiovascular disease risk. In the Coronary Risk Factors for Atherosclerosis (CORA) study, the comparison of clinical, biochemical, and lifestyle factors in 200 consecutive pre- and post-menopausal women with coronary heart disease to those in 255 age-matched population-based controls were performed [755]. The investigators observed that women with coronary heart disease compared with the control group were consuming a greater amount of animal fat and a smaller amount of fruits and vegetables. On the other hand, in the WHI trial (see page 125) was observed that aggressive lipid lowering treatment along with high consumption of fruits and vegetables did not significantly lower the clinical cardiovascular end points [731]. On the contrary, in the ERA study (see page 120) it was shown that women with higher saturated fat intakes had a lesser extent rate of progression of coronary atherosclerosis. Carbohydrate intake was strongly and positively associated with the progression rate of atherosclerotic lesions [715]. Moreover, the same study established that the greater consumption of fish and vegetables was correlated to less narrowed vessels (the mean diameter of the narrowing vessel was progressing slower) [716, 717] with fewer incidents of stenosis and fewer new atherosclerotic lesions.

Opposed to, in the Iowa Women's Health Study (see page 122) a positive

correlation between fish consumption and the cardiovascular disease outcomes was not established [719]. However, in the same study it was shown that the consumption of increased amounts of red meat was correlated with a higher risk of death, with the exception of deaths from cancer. The consumption of flavonoids and anthocyanins was also followed by a decreased risk of cardiovascular death [721]. Additionally, Akesson *et al.* [756] analyzed the data of 24,444 postmenopausal women without coronary heart disease from the Swedish Mammography Cohort Study. After 6.2 years of follow up 308 cases of myocardial infarction were reported. The authors observed that a healthy diet, a low to moderate alcohol consumption (≤ 5 g daily) and 3 determinants no smoking, waist/hip index <0.85 and physical activity (daily walking or bicycling for 40 minutes, and exercise 1 hour weekly) led to a 92% reduction of occurrence of myocardial infarction compared with women with a different lifestyle.

A healthy diet can affect the cardiovascular outcomes through a beneficial effect on lipid profile. There are classes of food, which exert a favorable effect on lipid profile. Gylling *et al.* [757] reported that women with or without coronary heart disease, who consume 3 g of plant sterols daily, had a reduction of plasma total cholesterol by 8.7-11%. This reduction remained even when the dose of sterols was reduced to 2 g daily (an amount, which has also been included in the guidelines). Also, Cleghorn *et al.* [758] found that plasma total cholesterol was reduced by 8.9% and LDL cholesterol by 12.3% in individuals who replaced butter with 2 g of plant sterols daily. Furthermore, Lukaczer *et al.* [759] compared postmenopausal women who additionally consumed in their usual healthy diet 4 g of plant sterols daily and postmenopausal women who followed only a typical healthy diet.

The investigators observed a reduction of plasma total cholesterol by approximately 16%, LDL cholesterol by 15% and triglycerides by 45% in the group who consumed plant sterols compared with the group of a usual diet. Moreover, Zern *et al.* [760] observed that grape polyphenols (antioxidative action) reduced plasma triglycerides by 6-15% in pre-menopausal and post-menopausal women and LDL cholesterol by 10% in premenopausal women. Despite some differences between relevant studies, most of them agree that a proper (healthy) diet favorably affects the cardiovascular disease outcomes and has been graded by

CHAPTER 6

Guidelines for Prevention of Cardiovascular Disease in Women

Abstract: The most common cause of death in menopausal women is cardiovascular disease with sudden death as the more severe complication. It is noteworthy to mention that two out of the three women who die suddenly, have been asymptomatic before.

More than one in three American women have some form of cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism). One in 31 women die of breast cancer, one in three die from cardiovascular disease.

This data led medical societies to suggest more intensive primary and secondary prevention of cardiovascular disease in women. The results from the Women's Health Initiative and Heart and Estrogen/progestin Replacement Study studies trigger a lot of discussion. Both unexpectedly reported an association between hormone replacement therapy and increased cardiovascular disease risk incidence.

Thus, the need for cardiovascular disease strategy prevention in women other than hormone replacement therapy, based on documented evidence and a critical review was required. The guidelines/scientific statements, which have been reported by various medical societies for the prevention of cardiovascular disease in women, will be analyzed.

Keywords: Cardiovascular disease prevention in women, Guidelines, Recommendations.

1. INTRODUCTION

As it was already stated in several chapters of this handbook, the most common cause of death in menopausal women is cardiovascular disease with sudden death as the more severe complication. It is noteworthy to mention that in the Framingham Heart Study [831, 832] two out of the three women who died suddenly, had been asymptomatic before.

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Also, women presenting acute coronary syndrome are the high risk population and in hospital mortality it remains higher for all age groups compared with men.

More than one in three American women have some form of cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) [833]. One in 31 women die of breast cancer, one in three die from cardiovascular disease.

This data led medical societies to suggest more intensive primary and secondary prevention of cardiovascular disease in women. In particular, that many physicians feel that the prevention in women could be delayed, due to later clinical development of cardiovascular disease in women, *i.e* 10 years later than men. What's more, the results from the WHI [727] and HERS studies [710] trigger a lot of discussion. Both unexpectedly reported an association between hormone replacement therapy and increased cardiovascular disease risk incidence.

Thus, the need for cardiovascular disease strategy prevention in women other than hormone replacement therapy, based on documented evidence and a critical review was required. The proper scientific interpretation and implementation aiming to improve preventive care in women was also necessitating. Furthermore, all existing evidence including male data should be modified before their inclusion into the process of women's guidelines formulation. Additionally, given that many patients do not have similar clinical profile to patients participating in clinical trials, conclusions should be drawn, regarding the potential similarities and generalization, from basic research to clinical practice.

An objective scientific collaboration among various medical associations created the guidelines for the prevention of cardiovascular disease in adult women with a broad range of cardiovascular risk.

It is noteworthy to mention that two decades after applying the most sophisticated techniques for the diagnosis of cardiovascular disease in its earlier stages, the classification as primary and secondary prevention has been less important. Instead, more significant is the grading of the cardiovascular risk and the identification of high risk groups.

The guidelines do not represent obligatory rules but aim to provide the physician with updated information regarding the severe problem that every aged woman is going to face and its prompt implementation.

The guidelines/scientific statements, cited in chronological order by the published year, which have been reported by various medical societies for the prevention of cardiovascular disease in women, will be analyzed below.

2. AMERICAN HEART ASSOCIATION SCIENTIFIC STATEMENT CARDIOVASCULAR DISEASE IN WOMEN, 1997

In this statement the role of major cardiovascular risk factors such as smoking, arterial hypertension (including isolated systolic hypertension), dyslipidemia, diabetes mellitus, obesity, sedentary lifestyle and unhealthy diet has been pointed out [834].

Smoking was considered to be the first reversible risk factor, responsible for >50% of myocardial infarctions in middle aged women [835]. Moreover, in this statement the fact emphasized was that cardiovascular risk factors 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 ageing women than in ageing men. Additionally, more than 52% of women, aged above 45 years, have an elevated arterial blood pressure and more than 40% of women, aged above 55 years, have increased blood total cholesterol concentration [834].

However, regarding the primary prevention, pharmacotherapy has been recommended only for the high risk group of patients and the change of lifestyle, like cessation of smoking, regular physical activities, maintenance of a normal body weight, and consumption of a diet containing low saturated fatty acids and an increase intake of fruits and vegetables, have been stressed. Concerning secondary prevention after a myocardial infarction, physicians should consult the guidelines, published in 1995 and 1996 for the management of patients with acute myocardial infarction [836 - 839]. According to these guidelines, the administration of b-blockers, angiotensin converting enzyme inhibitors (when the ejection fraction is <40%), aspirin and lipid lowering drugs were recommended.

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SUBJECT INDEX

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