

# I Brazilian Guidelines for Prevention of Cardiovascular Disease and Influence of Hormone Replacement Therapy in Climacteric Women

## Coordination

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At the end of this extensive and exhaustive work we are sure that this guideline offers good-quality orientation for Brazilian physicians to prevent cardiovascular diseases in climacteric women and correctly interpret the influence of HRT on the risk of these diseases. We want to express our deep gratitude to all colleagues who participated in this process for their contribution since the preliminary reports were elaborated until the active participation to obtain a consensus during the meeting held in São Paulo city on August 4, 2008. Similarly, we thank **Bayer Schering Pharma do Brasil** for their ethical attitude while giving unrestricted support, which was essential for us to accomplish this task.

### **The Coordinators**

## Introduction

Incidence of cardiovascular diseases (CVD) increased dramatically with ageing of the population, especially in women. According to data from the Brazilian Health Ministry, infarction and stroke are the main causes of death in women over 50 years. Although breast cancer is the main concern of women, it is known that the highest incidence of death in women is related to CVD (53%) as compared to breast cancer (4%). According to the Brazilian Institute of Geography and Statistics (IBGE) census of 2000, at the time of birth the estimated life for Brazilians is 68.6 years. In the last decade, this number experienced a gain of 2.6 years as related to 66 years, the estimated life for Brazilians in 1981.

Life expectancy has increased in both genders and at all ages. However, most expressive increases were observed in the female population. According to IBGE data (1991), women would live 7.2 years longer than men in Brazil. In 2000, the data indicated that this tendency had an increase of 7.8 years. The data also showed that 22% of the women (11% of the general population) were 45 years old or more, and 9.45% of the women (4.81% of the general population) had ages between 45 and 54 years. In this period, most women reach menopause, which remained constant at about 49–50 years. This means that, more and more, a greater number of women will live more in the postmenopausal period, which currently corresponds to about 1/3 of their lives. Data reported in 2005 indicates that life expectancy for Brazilian woman is already beyond 75 years.

In several countries such as the USA and Brazil, CVD remain as the main cause of morbidity and mortality among women, especially those with age above 50 years. Among them, more deaths are due to CVD (41.3%) than to the following seven combined cases of death. The risk of death due to CVD is six-fold higher than that of breast cancer. Since the 1960s, CVD are also in the first place among the causes of mortality for both men and women in our country.

Recent data from the American Heart Association (AHA) show that only 46% of the women know this fact although this rate has increased since 1997 when it was about 30%.

On the other hand, there is currently a great concern for the effects of hormone replacement therapy (HRT) on menopausal women or those in the menopausal transition regarding the risk of CVD. This concern is not purposeless because such diseases are the leading cause of mortality during this period of women's life.

In the medical literature, HRT has well-defined and consensually accepted indications for alleviation of climac-

teric symptoms, prevention and treatment of urogenital atrophy, and prevention of the main consequences due to the hypoestrogenemia characteristic of this age period of women. It should emphasize that there are currently few contraindications to this therapeutic modality. Personal antecedents of breast cancer, severe liver or kidney failure, and hormone-related thromboembolism are included among them.

HRT has been considered to increase CVD in the too many publications of the Women's Health Initiative (WHI) study (since the first one in the middle of 2002), particularly when conjugated equine estrogens and medroxyprogesterone acetate are associated. The extent of this study has led many physicians interested in this issue to consider that the results contained therein should be validated for all HRT formulations with their different and countless possibilities of composition, doses, and routes of administration.

In the years that followed the original publication of the WHI study, criticisms accumulated regarding the criteria for selection of the studied sample, mean age of the patients included and the estrogen-progestative formulation used, and the extrapolation of its results to patients with different ages and in different moments of the postmenopausal period, and different HRT formulations. These are known to consist of different hormones, doses, and routes of administration.

Consensuses or guidelines have been established by international societies who wished to offer guidelines regarding the relationship between HRT and cardiovascular risk. During this year, publications by the AHA, North American Menopause Society (NAMS), and International Menopause Society (IMS) make a clear reference to the issue although not specially dealing with the influence of HRT on the risk of CVD.

The article "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update" published by the AHA states that HRT should not be used in primary or secondary prevention of CVD (Class III, Level A).

The NAMS consensus recognized that most preclinical and observational studies support the idea of a benefit from isolated and progestogen-associated therapy for risk reduction of coronary heart disease (CHD). On the other hand, most randomized clinical studies do not confirm this statement. Current studies suggest that these different findings may be related to the moment of therapeutic intervention regarding menopause.

Recommendations of the IMS board include a statement that users with a late start of the HRT may have a slight and transient increase in the risk of coronary events. It is considered that risk of stroke has a direct relationship

with age, and users of HRT over 60 years old may have this risk increased.

However, none of these institutions approached the issue in its intimacy, considering the singularity of each therapeutic regimen, composition of the different therapeutic formulations available, individuality of each patient, time of menopause elapsed, patients' age, and clinical judgment in the vast material published after the WHI study. On the other hand, it should be emphasized that clinical judgment should not consider solely and exclusively the evidence gathered by randomized and placebo-controlled clinical tests, but the whole set of clinical variables and risk factors presented by the patient evaluated regarding her eligibility or not for HRT. As already mentioned, its involvement is not restricted to the influences it has on the risks of CVD.

The recommendation degrees and levels of evidence shown in Table 1 were used in this Guideline.

### Cardiovascular risk in climacteric women

Although coronary artery disease (CAD) increases with age in the population, its clinical manifestations in women appear on average 10 to 15 years later than in men. This difference is possibly explained by estrogenic protection. Perhaps because of this fact, women (and certainly some health professionals) believe that preventive measures may also be postponed, which is a mistake since the determinant atherosclerotic process in the main cardiovascular risk factors involved is already evident since 20 years old.

Indeed, occurrence of CAD in postmenopausal women is 2–3-fold higher than in premenopausal ones of the same age range. One in nine women between 45–64 years has some form of CVD whereas this ratio changes to 1 in 3 after the age of 65. At each decade of life, mor-

tality rate has a 3-5-fold increase in the female gender. Studies published in the 1950s and 1960s state that early menopause is associated with increase in CAD. The Framingham study compared the incidence of CVD in pre- and postmenopausal women of four different age ranges and showed that the younger the woman the higher the risk of CVD for those in the climacterium. This risk decreased in older age ranges indicating the great impact of menopause on younger women.

In occidental countries, a decline in mortality rates due to CVD (cardiac and cerebrovascular) was observed in the last decades. However, such decline was steeper in the male than in female population. In Brazil, although a reduction occurred in the rate of CVD, a tendency towards stabilization of the mortality rate due to the ischemic heart disease was observed. Lotufo and coworkers compared women from different countries and showed higher mortality rates due to ischemic heart disease in women living in Brazilian capitals. Mansur and coworkers showed that a tendency towards a decrease in mortality rates due to CVD was observed in the southern and southeastern states of Brazil. On the other hand, a tendency towards an increase was observed in the states of the mid-western, northern, and northeastern regions. In 2004, mortality rates for women older than 30 years due to stroke and myocardial infarction were 105 and 87 per 100,000 inhabitants, respectively (DATASUS).

Several factors are related to this high cardiovascular risk and the greater the number of risk factors present, the greater the chance to present a cardiovascular event. Similarly, the better the control of lifestyle, with a reduction in the number of modifiable factors associated, the greater the reduction in this risk. The Nurses' Health Study evaluated more than 84,000 healthy American women for 16 years and showed that changes in lifestyle may prevent over 80% of the coronary events.

Data from the AHA show that about 60% of women lack sufficient knowledge about CVD, although more than 90% of them recognize that regular physical activity, weight loss, stress control, and healthier feeding habits (with salt and cholesterol reduction in the diet) are important measures to reduce cardiovascular risk.

Thus, provided that the prevention measures are started as early as possible, a better understanding of the role of these risk factors will allow interference with the natural history of emergence and progression of these atherosclerotic diseases.

The classical Framingham Heart Study classified the risk of "death or presenting a coronary event in the following 10 years" as high (above 20%), intermediate (between 10 and 20%), or low (below 10%) based on the presence

**Table 1. Recommendation grades and evidence levels.**

#### Recommendation grades

- I. There are consensus and evidence in favor of the indication
- IIa. There is divergence, but most approve
- IIb. There is divergence and division regarding opinions
- III. Not recommended

#### Evidence levels

- A. Multiple controlled randomized clinical trials
- B. A single controlled randomized clinical trial, non-randomized clinical studies, or well-designed observational studies
- C. Series or case reports
- D. Consensus of specialists

of risk factors such as age, level of total cholesterol, HDL-cholesterol, blood pressure level, and smoking habit. Regarding diabetes, the Framingham study clearly showed that the risk factor plays a more significant role in women than in men, and the relative risk had approximately 5- and 2-fold increases in the former and the latter, respectively, as compared to those without this disease. Presence of diabetes allows patients to be classified as being at high risk for cardiovascular events independent of the presence of other risk factors.

In the last decades, risk factors including physical inactivity, obesity, and excessive alcohol consumption were considered independent determinants of high cardiovascular risk in both men and women.

A recent epidemiologic study (Inter Heart Study) identified the risk factors for myocardial infarction in several populations of the world. It was observed that the risk factors are the same for both men and women but the impact of systemic arterial hypertension (AH) or diabetes mellitus in women is greater than in men. On the other hand, the protecting impact of physical exercises and moderate alcohol intake in women is more evident than in men. It is noteworthy that the modifiable risk factors constituted 94% of the risk of myocardial infarction in the female population of the study.

## Cardiovascular risk factors

### Smoking

According to the IBGE data (1991), the prevalence was 24% in people aged above 5 years, with higher concentration between 30 and 49 years of age. Other studies conducted between 1971 and 1988 showed prevalence rates ranging from 35 to 40%. Recently, the Transversal Study of the São Paulo State Society of Cardiology (1999) evaluated about 20,000 individuals in 19 cities and a prevalence rate of 17% was observed for smoking.

Death rate due to CVD increases 31% among women exposed to tobacco either at work or at home, and this is considered the main modifiable risk factor for cardiovascular morbidity and mortality. About 33.5% of cardiovascular deaths that occurred in the USA between 1995 and 1999 were related to smoking and recent data show that about 21% of the American women are smokers.

The Nurses' Health Study showed that death risk due to CAD were 2-fold higher in those smoking 1–4 cigarettes/day and 5.5-fold higher in women who smoked 25 cigarettes/day as compared with non-smokers.

### Dyslipidemia

Several studies show increased risk of CVD in women with elevated total cholesterol (TC) and LDL-cholesterol.

However, low HDL cholesterol become an independent risk factor for CAD in women when its levels are somewhat below 50 mg/dL and with high triglyceride levels, especially in the age range 50–69 years and in diabetic patients.

According to the National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) III, levels of triglycerides  $\geq 150$  mg/dL and HDL  $\leq 50$  mg/dL are components of the metabolic syndrome, and its impact on CVD incidence is greater in women (especially those in the menopausal phase) in comparison with men<sup>12,13</sup>.

Recent data from the AHA show that about 48% of American women present dyslipidemia and, although cholesterol increase is related to the cause of death in about 31% of them, only 1% of them consider increase in triglyceride levels a risk factor.

Total serum cholesterol levels (TC) were measured by Martinez et al. (2002) in 39,768 subjects living in selected capitals of Brazil and great cities of São Paulo state. In the study, the women were  $45.9 \pm 16.4$  years old and their mean cholesterol level was  $201 \pm 35$  mg/dL. The rate of women with total cholesterol above 200 and 240 mg/dL was 42 and 15%, respectively. For all risk levels, cholesterol level in women was higher than in men.

### Sedentariness

In the USA (2001), prevalence of sedentariness in women were 36.2 and 55.2% for the white and black ethnicities, respectively. These prevalences are higher than those in the male gender (32.5 and 44.1%, respectively).

Recent data show that only 28% of the American women perform exercises more than 3 times a week and 1 in 5 women never practiced any aerobic physical activity.

Risk of CAD related to sedentariness ranges from 1.5 to 2.4, which is comparable to those for arterial hypertension, dyslipidemia, and smoking.

Aerobic physical activity of moderate intensity may have an impact on reduction of the cardiovascular event risk on the range from 30 to 40% when performed regularly, at a minimum of 30 minutes a day at least 3 times a week.

### Overweight, obesity and metabolic syndrome

Approximately 32% of the Brazilian population is overweight [(Body Mass Index (BMI)  $\geq 25$  kg/m<sup>2</sup>], and the specific rates are 38 and 27% for the female and the male genders (Ministry of Health, 1993). Obesity (BMI  $> 30$  kg/m<sup>2</sup>) was found in 8% of the Brazilian population.

In the USA (2001), women had prevalence rates of 61.9 and 30.5% for overweight and obesity and for isolated obesity, respectively; in black women this rate was higher than 80%. In this country, more than 50% of the women over 40 years are obese and more than 80% are overweight.

In the USA, prevalence of metabolic syndrome in adults is 23.7%, with similar values for men (24.0%) and women (23.4%). Its presence increases the risk of diabetes mellitus and CVD, as well as mortality due to cardiovascular and all causes.

In the climacterium, there is an increase in body weight related to reduction in the basal metabolism, reduction in regular physical activity, and increase in caloric food intake and depression. Regarding body weight reductions, about 5–10% of them are already associated with reduction in the cardiovascular risk, especially because they favorably affect factors including cholesterol levels and blood pressure.

### Diabetes mellitus

Based on the Brazilian Diabetes Consensus (1980), the age-adjusted (30–69 years) prevalence was 7.6% with a 5–10% variation according to the state capital evaluated, with equal distribution between genders.

In the USA, prevalence of diabetes mellitus reached levels of 7.3% in 2002, having increased 54% between 1994 and 2002 (about 61% since 1990 and about 8.2% between 2000 and 2001), with a much higher impact on CVD for the female gender.

Diabetes mellitus causes the risk of CAD in women to be 3- to 7-fold greater as compared with that in non diabetics, differently from men for whom the risk is only 2- to 3-fold greater. It also causes the risks of cerebrovascular accident and peripheral vascular disease to be 1.8- to 6-fold greater.

Not only the established diabetes mellitus symptoms but also glucose intolerance, insulin resistance, and hyperinsulinemia increase CVD occurrence, and serum insulin level is identified as an independent risk factor for CAD.

Presence of CVD adjusted for age in diabetic women is twice as high as in women without diabetes, and the rates for hospitalization and cardiac death are 4 and 3- to 6-fold higher, respectively.

### Arterial hypertension

Prevalence of arterial hypertension (AH) in the Brazilian adult population was estimated to be 15% according to the Ministry of Health (1991) and IBGE (Population Census, 1991). However, transversal studies revealed higher rates in Rio de Janeiro city (1990) and São Paulo state (25%).

AH prevalence increases progressively with age, being above 50% in the elderly. A higher proportion of men have AH up to the age of 55 years; the proportion of women is slightly higher from 55 to 74 years and predominance of the female gender is significantly greater over 75 years

of age<sup>1</sup>. Thus, about 88% of women will eventually develop AH in the menopausal phase, and HA incidence increases both with age and the beginning of the post-menopausal phase.

AH contributes with about 35% of all cardiovascular events and approximately 45% of undiagnosed infarction cases in women, and 4-fold elevation of CAD risk as compared with normotensive women.

Often in metabolic syndrome, association of risk factors such as dyslipidemia, insulin resistance, glucose intolerance, and abdominal obesity increases its atherogenic potential, and it has been considered one of the most important mechanisms of CVD in women. Thus, pharmacologic antihypertensive treatment, concomitant with the changes in lifestyle mentioned herein, has been shown to be a significant intervention in preventing coronary events in hypertensive women.

### Other factors

In the last decade, other factors such as high-sensitivity C-reactive protein (hs-CRP), homocystein, lipoprotein (a), and fibrinogen showed a marked influence on the female gender. However, it is not clear if control of these factors reduces cardiovascular risk.

## Scientific evidence of impact in clinical practice

### Importance of clinical outcomes

Scientific evidence, which determines changes in clinical practice, should be based on health-disease outcomes such as death and disease incidence. Data from studies that interfere with substitute outcomes (pathophysiological and biochemical markers, etc) have less direct impact on clinical practice, although they may be relevant to a better knowledge of the disease and diagnostic and therapeutic development.

### Risk stratification and lipid goal for prevention and treatment of atherosclerosis

Acute coronary event is the first manifestation of atherosclerotic disease in at least half of the individuals presenting this complication. In this way, identification of asymptomatic individuals with a higher predisposition is crucial for an effective prevention with a correct definition of therapeutic goals. Risk estimate of the atherosclerotic disease results from the sum of risks caused by each risk factor, plus potentiation caused by a synergism between some of these factors. In view of the complexity of these interactions, subjective assignment of risk frequently results in under- or overestimation of cases of higher or lower risk, respectively. In order to by-pass this difficulty, different algorithms based on regression analysis of popu-

lation studies were created through which identification of global risk is substantially refined. The Framingham Risk Score (FRS) algorithm was adopted in this Guideline although others exist. In this score, probability of occurrence of myocardial infarct or death due to coronary disease in a period of 10 years is estimated for individuals without prior diagnosis of clinical atherosclerosis. Although this risk estimate is subject to correction according to epidemiological indicators of the studied population, FRS adequately identifies individuals with high and low risk.

### Risk stratification

Risk stratification should be performed in three phases. Phase 1: identification of presence of atherosclerosis. Phase 2: application of Framingham Risk Score (FRS). Phase 3: identification of aggravating factors that worsen classification regarding risk when present.

#### Phase 1 – Presence of significant atherosclerotic disease or its equivalents

As mentioned above, risk of atherosclerotic disease is estimated based on the joint analysis of characteristics that increase the probability of the subject of developing the disease. Therefore, previous manifestation of the disease itself is the clearest identifying factor of risk. In this way, identification of clinical manifestations of the atherosclerotic disease or its equivalents, such as presence of type 1 or 2 diabetes mellitus, is the first step in risk stratification (Table 2). Individuals thus identified have a higher than 20% risk of presenting new cardiovascular event in 10 years (Recommendation Degree 1, Level of Evidence A).

#### Phase 2 – Risk score

Among individuals without significant atherosclerotic disease, those with low and high risk (less than 10% and over 20% probability of infarction or death due to coronary disease in a 10-year period, respectively) may be estimat-

**Table 2. Criteria for the identification of patients at high risk for coronary events (Phase 1).**

- Present manifest or previous Coronary Artery Disease (stable angina, silent ischemia, acute coronary syndrome, or ischemic cardiomyopathy)
- Arterial Cerebrovascular Disease (ischemic stroke or transient ischemic attack)
- Aneurysmal or stenotic disease of the abdominal aorta or its branches
- Peripheral arterial disease
- Carotid Artery Disease (Stenosis  $\geq 50\%$ )
- Type 1 or 2 diabetes mellitus

ed by FRS. For individuals classified by FRS as having intermediate risk (between 10% and 20% of infarction or death due to coronary disease in a 10-year period), more attention should be paid to aggravating factors (Phase 3) in order to improve FRS accuracy. Criteria for calculation of risk using the FRS are shown in Table 3.

**Metabolic syndrome** – Excess weight associated with fat accumulation in the mesenteric region (called central, visceral, or androgenic obesity) is associated with higher risk for atherosclerotic disease. Measurement of waist circumference allows us to identify patients with this form of obesity, which should be assessed with the patient in the standing position, at end of expiration, in the middle point between the last costal arch and the anterosuperior iliac crest, with an inelastic tape measure in the horizontal position. Usually these individuals present dyslipidemia (elevated triglycerides, low HDL-C, small and dense LDL particles, postprandial hyperlipidemia, insulin resistance, and systemic arterial hypertension, which characterize metabolic syndrome when present together. Criteria of the Internal Diabetes Federation (IDF) were adopted in the present Guideline, with differentiated values for fasting glycemia and waist circumference, considering the different ethnicities (Table 4). FRS should also be used in patients with metabolic syndrome who do not present significant atherosclerotic disease or its equivalents. However, presence of metabolic syndrome is an aggravating factor for patients in any risk category according to Table IV (Recommendation Degree IIa, Level of Evidence B).

Diagnosis of metabolic syndrome requires the presence of abdominal obesity as an essential condition and two or more criteria shown in Table 4.

#### Phase 3 – Aggravating factors

In the evaluation of short-term cardiovascular risk for the young and women, risk estimates of coronary events using FRS are less precise in subjects at intermediate risk (in which most events occur). Table 5 shows proposed aggravating factors that can take a subject to the immediately category of risk. Intermediate-risk patients or those at low risk but presenting aggravating factors may be reclassified into a risk category above that estimated using the FRS alone (Recommendation Degree IIa, Level of Evidence B).

Use of biochemical and/or imaging tests (ultrasound (US) of the carotid arteries for assessment of the intima-media thickness (IMT) or computed tomography (CT) for calculation of the coronary calcium score) are not advocated as routine tools for risk stratification and detection of subclinical atherosclerosis. However, they may be used specifically in subjects who present a family history of early atherosclerotic disease or are considered to be of

**Table 3. Framingham risk score for calculation of risk of myocardial infarction or death in 10 years in women.**

Age	Points	Total cholesterol (mg/dL)					Smoking		Total points woman	10-y absolute risk (%)
		<160	160-199	200-239	240-279	≥280	No	Yes		
20-34	-7								< 9	< 1
35-39	-3	0	4	8	11	13	0	9	9	1
40-44	0	0	3	6	8	10	0	7	10	1
45-49	3	0	3	6	8	10	0	4	11	1
50-54	6	0	3	6	8	10	0	4	12	1
55-59	8	0	3	6	8	10	0	4	13	2
60-64	10	0	1	2	3	4	0	2	14	2
65-69	12	0	1	2	3	4	0	2	15	3
70-74	14	0	1	1	2	2	0	1	16	4
75-79	16	0	1	1	2	2	0	1	17	5
									18	6
									19	8
									20	11
									21	14
									22	17
									23	22
									24	27
									≥25	≥30

SBP (mmHg)	Not treated	Treated	HDL-C (mg/dL)	Points	Total points woman	10-y absolute risk (%)
< 120	0	0	≥60	-1	21	14
120-129	1	3	50-59	0	22	17
130-139	2	4	40-49	1	23	22
140-159	3	5	≤40	2	24	27
≥160	4	6			≥25	≥30

Obs: women who smoked more than one cigarette in the last month are considered smokers. Subjects in use of antihypertensive medication are considered to have 'treated hypertension'.

**Table 4. Diagnostic criteria for metabolic syndrome.**

Criteria	Definitions
<b>Abdominal obesity</b>	<b>Waist circumference (cm)</b>
Men	
White of European origin and black	≥94
South-Asian, Amerindian, and Chinese	≥90
Japanese	≥85
Women	
White of European origin and black	≥80
South-Asian, Amerindian, and Chinese	≥80
Japanese	≥90
<b>TG</b>	≥150 mg/dL or treatment for hypertriglyceridemia
<b>HDL-cholesterol</b>	<b>(mg/dL)</b>
Men	<40
Women	<50
<b>Blood pressure</b>	<b>(mm Hg)</b>
Systolic, or	≥130 or treatment for AH
Diastolic	≥85 or treatment for AH
<b>Fasting glycemia</b>	≥100 mg/dL or treatment for DM

Metabolic syndrome diagnosis includes presence of abdominal obesity as an essential condition, and two or more of the above criteria. AH=arterial hypertension; DM=diabetes mellitus.

**Table 5. Aggravating risk factors.**

- Family history of premature coronary disease (first-degree relative, male <55 years or female <65 years)
- Metabolic syndrome
- Micro- or macroalbuminuria (>30 µg/min)
- Left ventricular hypertrophy
- Chronic renal failure (creatinine ≥1.5 mg/dL or creatinine clearance <60 ml/min)
- Highly sensitive C-reactive protein >3 mg/L (in the absence of non-atherosclerotic etiology)
- Evidence of subclinical atherosclerotic disease by
  - Coronary calcium score >100 or >75<sup>th</sup> percentile for age or sex or
  - Carotid thickening (IMT) maximum >1 mm or
  - Ankle-brachial index <1.9

intermediate risk according to the FRS (Recommendation Degree IIa, Level of Evidence B).

In the particular group of women, menopause (mainly when it occurs early) and hypoestrogenemia are accompanied by increase in risk of CVD. Nevertheless, hypoestrogenemia as an aggravating factor able to shift a woman to a higher risk category as calculated by FRS was not a consensus among coordinators.

Atheroma plaques in the aorta as identified by the US test (as a routine gynecologic examination) is another consideration that deserves to be mentioned. Such finding may indicate that this particular patient has a higher risk.

### Therapeutic goals and risk reevaluation

All patients with isolated dyslipidemia and those with increased cardiovascular risk should be advised to adopt non-pharmacologic measures related to lifestyle change (LSC) (Recommendation Degree I, Level of Evidence A). Pharmacological treatment should be started in those at low or intermediate risk (6 or 3 months afterwards, respectively) who did not meet the goals (Table 6) after non-pharmacological measures. In high-risk subjects, non-pharmacological measures and treatment with hypolipidemic drugs should be started simultaneously. In patients with significant atherosclerotic disease, obtention of LDL-C level ≤ 70 mg/dL leads to additional reduction in the incidence of cardiovascular events according to present evidence. Therefore, the present Guideline recommends the goal of LDL-C ≤ 70 mg/dL for all individuals with significant atherosclerotic disease (Table 7; Recommendation Degree I, Level of Evidence A).

Hypolipidemic drugs should always be used when LSC effect is not satisfactory or cannot be awaited due to clinical

**Table 6. Initial therapeutic measures and reevaluation period.**

Strata	Initial therapeutic measures	Reevaluation of goals
Low risk	TLC	6 months
Intermediate risk	TLC	3 months
High risk	TLC + pharmacologic treatment	3 months
Manifest atherosclerosis	TLC + pharmacologic treatment	Individualized

TLC=therapeutic lifestyle changes.

**Table 7. Goals for preventive therapy with hypolipidemic drugs.**

10-year risks	Therapeutic goals (mg/dL)	
	LCL-C*	Non-HDL-C
Low risk	<10%	<160
Intermediate risk	10 to 20%	<130
High risk or diabetics	>20%	<100 (optional <70)
Significant atherosclerosis	<20%	<100 (optional <100)
	<b>HDL-C</b>	<b>TG</b>
Men	≥40	<150
Women	≥50	<150
Diabetics	≥50	<150

\*Estimated by the Friedewald equation; obs: when the goals are not attained, obtention of the greatest possible reduction is recommended.

**Table 8. Statin doses and effects on LDL-C.**

Drugs	Doses (mg)	Δ LDL-C (%)
Simvastatin	20 to 80	-27 to 42
Lovastatin	10 to 80	-21 to 41
Pravastatin	20 to 40	-20 to 33
Fluvastatin	20 to 80	-15 to 37
Atorvastatin	10 to 80	-37 to 55
Rosuvastatin	10 to 40	-43 to 55

priority. Choice of the therapeutic class is conditioned to the existing hyperlipidemia.

In isolated hypercholesterolemia, statins are the recommended drugs, which can be administered in association with ezetimibe, cholestyramine, and eventually fibrates or nicotinic acid.

Statin should be orally administered in a daily single dose, preferably in the evening in the case of short half-life drugs or at any hour for those with a longer half-life

such as atorvastatin and rosuvastatin. The therapeutic effect will be maintained only with daily doses, and the drug should not be discontinued or used on alternate days, except for the presence of side effect or clinical contraindication. The recommended doses and the expected reduction in LDL-C are found in Table 8.

Adverse effects are rare during treatment with statins. The most severe, such as hepatitis, myositis, and rhabdomyolysis, are observed even more rarely. However, determination of basal creatine phosphokinase CK and transaminase (especially ALT) levels and repetition at the first reevaluation or at each dose increase are recommended in order to identify possible adverse effects.

Careful monitoring of patients who have muscle pain and/or 3- to 7-fold increase in the upper limit of normality (ULN) for CK, is recommended. Statins should be discontinued if one or more of the following situations occur: progressive CK increase, CK increase above 10-fold the ULN, or persistence of muscle symptoms. In these cases, the same statin may be restarted at a lower dose or another statin may be tried after normalization of the disorder that led to discontinuation.

For further details on hypolipidemic drugs that preferentially act on triglycerides or HDL-cholesterol, readers are referred to seek information in the IV Brazilian Guideline for Dyslipidemias and Prevention of Atherosclerosis.

### **New evidence for risk stratification in women – new scores**

In view of recent evidence that the FRS has limitations, mainly in women, it is clear that: a) although risk in women may be low in 10 years, it is usually a lifetime risk when 1 in 2 women will have a cardiovascular event; b) a high percentage of women have a cardiac event even if classified as of low or intermediate risk; risk factors such as family history and subclinical disease are not taken into account.

For these reasons, the recent revision of the American Heart Association Guidelines reclassified the female population into three strata; high risk, at risk, and low risk. Risk stratification reevaluations of the female population will continue in the future.

### **Summary of recommendations for cardiovascular prevention in women**

#### **Clinical recommendations for prevention**

##### **1. Interventions in lifestyle**

a) Smoking – Women should discontinue tobacco use; pharmacologic therapy or temporary nicotine replacement should be used to achieve this goal if necessary (Class I, Level B).

b) Physical activity – Women should perform at least

30 minutes of moderate physical activity 3 to 6 times a week (Class 1, Level B). If weight loss is the goal, time of exercise should reach from 60 to 90 minutes a day (Class I, Level C).

c) Rehabilitation – Should be considered in all patients who had a cardiovascular event (Class I, Level C).

d) Diet – Consumption of a diet rich in fruits, fibers, and vegetables should be stimulated; fish should be consumed at least twice a week (Class 1, Level B). Saturated fats should compose 10% of the total daily energy, at most, and trans fats should be avoided (Class 1, Level B). Alcohol consumption should be limited to a maximum of 1 drink per day (Class 1, Level B). Since soy protein intake (25 g/day) may reduce plasma cholesterol (–6% LDL-C), consumption of soy protein can be considered an auxiliary treatment of hypercholesterolemia (Recommendation Degree IIa, Level of Evidence B).

e) Omega-3 fatty acids are cold and deep water fish oil derivatives, which reduce liver TG synthesis. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derivatives are the most important of this class. In high doses (4 to 10 g daily), they reduce triglyceride and slightly increase HDL-C levels. However, they may increase LDL-C levels. In those with CAD, supplementation with omega-3 (1 g/day; capsules) causes a 10% reduction in CVD (death, myocardial infarction, stroke). Therefore, omega-3 fatty acids can be used as an adjuvant therapy in hypertriglyceridemia or as a substitute for fibrates, niacin, or statins in intolerant patients (Class IIb, Level B).

f) Depression – Consider the hypotheses of diagnosis and referral for treatment of the cases (Class IIa, Level B).

### **2. Intervention in risk factors**

a) Blood pressure (BP) optimal level – Encourage levels of BP <120/80 mm Hg through weight control, healthy diet, physical activity, moderate alcohol consumption, and sodium restriction.

b) Blood pressure (BP) – Pharmacotherapy is indicated when BP ≥140/90 mm Hg or even at lower levels (≥130/80 mm Hg) when chronic renal disease or diabetes are concomitant. Drugs such thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB) may be recommended initially according to specific indications (Class I, Level A).

c) Lipids and lipoprotein levels – Ideal levels together with lifestyle measures: LDL-cholesterol (LDL-C) <100 mg/dL, HDL-cholesterol (HDL-C) >50 mg/dL, and triglycerides (TG) <150 mg/dL should be encouraged (Class I, Level B).

d) Lipids - Pharmacotherapy

• Women at high risk should receive therapy in order to

maintain their levels of LDL-C <100 mg/dL (Class I, Level A). Optionally, levels <70 mg/dL may be reached in women with manifest atherosclerotic disease (Class IIa, Level B).

- Women at intermediate risk or with multiple risk factors should receive pharmacotherapy if they have levels of LDL-C  $\geq$ 130 mg/dL (Class I, Level B). Women at low risk (<10% according to Framingham Risk Score but with risk factors should receive pharmacotherapy if LDL-C  $\geq$ 160 mg/dL (Class I, Level B).

- Women without risk factors should receive pharmacotherapy if LDL-C  $\geq$ 190 mg/dL (Class I, Level B).

e) Diabetes – Adequate measures should be taken for glycemia control, and maintenance of Hb A1c <7% if possible (Class I, Level B).

### 3. Preventive measures

a) Acetylsalicylic acid (ASA) should be indicated at doses [in the range] of 75 to 325 mg/day for all high-risk patients (Class I, Level A). If there is intolerance to ASA, 75-mg/day clopidogrel may be used (Class I, Level B).

b) ASA may be indicated for women  $\geq$ 65 years if risk for digestive bleeding is lower than that for stroke (Class IIa, Level B).

c) Betablockers should be used for indefinite time in all cases of myocardial infarction, acute coronary syndrome, or ventricular dysfunction except when there are contraindications (Class I, Level A).

d) Angiotensin-converting enzyme inhibitors (ACEI) and ARB – ACEI should be used in women after myocardial infarction and in those with ventricular dysfunction or diabetes mellitus (Class I, Level A). ARB may be another option (Class I, Level B).

e) Aldosterone blockers – ACEI should be used in patients with ventricular dysfunction (EF <40%) in use of adequate medication for cardiac failure and without contraindication to its use (Class I, Level B).

### Class III interventions (not useful and potentially damaging) in prevention of cardiovascular diseases in women

1) Antioxidant supplements such as vitamins C and E and beta-carotene (Class III, Level A).

2) Folic acid associated or not with vitamins B<sub>6</sub> or B<sub>12</sub> (Class III, Level A).

3) ASA in women <65 years (Class III, Level B).

### Hormone replacement therapy

Decline in plasma estrogen levels is observed in all women who pass through the menopausal transition. This period makes many, but not all, women suffer from symp-

toms of this period, of which the vasomotor ones (called hot flashes) are the most characteristic and denouncers of the subjacent hormonal deficit. HRT is considered the best treatment for this train of symptoms (Class I, Level A), therefore being very frequently indicated as a therapeutic measure for alleviation of symptoms in this stage of life. Moreover, it offers considerable benefits to the patient's quality of life.

On the other hand, together with alleviation of climacteric symptoms, HRT has many other effects on organs and systems of the female body that may bring beneficial and detrimental consequences to its users.

In harmony with this variety of systemic effects, and regarding that assistance to women in the climacteric period should be multidisciplinary, specialists who attend women at this stage of life are recommended to be familiar with this therapeutic modality. In addition, it is important that physicians involved in the clinical follow-up of climacteric women know that the HRT label comprises various therapeutic options, and different administration routes and hormonal association regimens. Any of these HRT options may have a different effect on the health of a woman who intends to use HRT. Therefore, it is recommended that one should not generalize regarding HRT effect without specifying the therapeutic regimen and hormones used.

Appropriate terms must be used to express time periods and true characteristics of this stage of life, as follows:

**Climacterium** – The period in women's life between the end of their reproductive phase and the beginning of senescence (40–65 years of age).

**Menopause** – Date by the time of the last spontaneous menstruation (occurs about 50 years).

**Perimenopause** – It is the variable period in each woman's life that starts with menstrual irregularities and extends to twelve months after the beginning of menopause. A period of two to four years since the beginning of menstrual irregularities before menopause until its cessation.

**Menopausal transition** – The meaning of this period may be confused with that of perimenopause, which includes the year following menopause. Although both begin at the same time point, menopausal transition finishes earlier, when menopause terminates.

**Postmenopause** – Is the time elapsed after occurrence of menopause. It is divided into recent (the first five years) and late menopause.

HRT was first introduced for the treatment of menstrual disorders, climacteric symptoms (vasomotor disorders, such as hot flashes and sudoresis), and urogenital atrophy (vaginal dryness and dyspareunia; Class I, Level A). Since secondary benefits of this therapy could be observed in the clinical use, indications of HRT widened along time.

HRT is not an isolated nor the only measure. It should be part of a global strategy, which includes recommendations on lifestyle, diet, exercises, smoking, and alcohol consumption, to maintain women's health in the postmenopause. HRT should be individualized and adjusted according to the symptoms, prevention needs (according to the personal and family history), results of pertinent investigation, woman's preference, and her expectations.

HRT includes various hormone products, which are used at different doses, regimens, and administration routes; the different potential risks and benefits should be known by medical professionals.

Therefore, it is recommended that a uniform terminology be established regarding the different HRT regimens used in the climacterium period, as follows:

- ET: Estrogen therapy alone;
- Natural progesterone;
- EPT: Combined estrogen-progestogen therapy;
- CC-EPT: Combined continuous estrogen-progestogen therapy;
- CS-EPT: Combined sequential estrogen-progestogen therapy (daily estrogen and sequentially added progestogen therapy);
- HRT: Hormone replacement therapy - generic denomination that does not specify the therapeutic regimen (applied indistinctly to all forms of ET and EPT);
- HRT users should have at least one annual visit including physical examination, medical history update, pertinent laboratory tests, and imaging investigation besides a discussion on their lifestyles.

HRT should be recommended with a clear indication regarding its use. Besides its classical proposal for alleviation of the climacteric symptoms and urogenital atrophy, it may have the following indications:

- - Protection against collagen loss and skin atrophy (Class I, Level A);
- - Conservation of bone mass and reduction in the risk of fractures (Class I, Level A);
- - Probable reduction in the risk of Alzheimer's disease (when started at the perimenopause or in women in recent postmenopause) (Class IIb, Level A);
- - Improvement in well-being and sexuality (Class I, Level A);

The minimum HRT dose required to maintain efficacy should be used.

### Estrogens

Basically, HRT consists of estrogen replacement. These hormones should be used alone in climacteric

women without uterus (except for severe cases of previous endometriosis, endometroid carcinoma, ovary carcinoma, endometrial adenocarcinoma treated for less than five years) and when hysterectomy was not total, i.e., in presence of a residual endometrium. In these circumstances, progestogen should be associated.

Estrogen doses used in HRT are sufficient to maintain plasma levels able to alleviate vasomotor symptoms, revert urogenital atrophy, and prevent osteoporosis. The estrogens used in HRT are estradiol, conjugated equine estrogens, estriol, and promestriene. The two last ones are destined to vaginal use.

Obtention of plasma estrogenicity sufficient to achieve the goals established with their indication is the common objective shared by the different forms of estrogen administration. The current basic rule is the administration of doses as low as possible to achieve these objectives. However, notwithstanding this central objective, the different possibilities of administration, the use of different estrogens and distinct therapeutic regimens, in association or not with progestogens, may produce singular metabolic and vascular effects. Therefore, it should be remembered that the different estrogens, doses, administration routes, and therapeutic regimens have not the same and uniform effects on cardiometabolic and vascular risks.

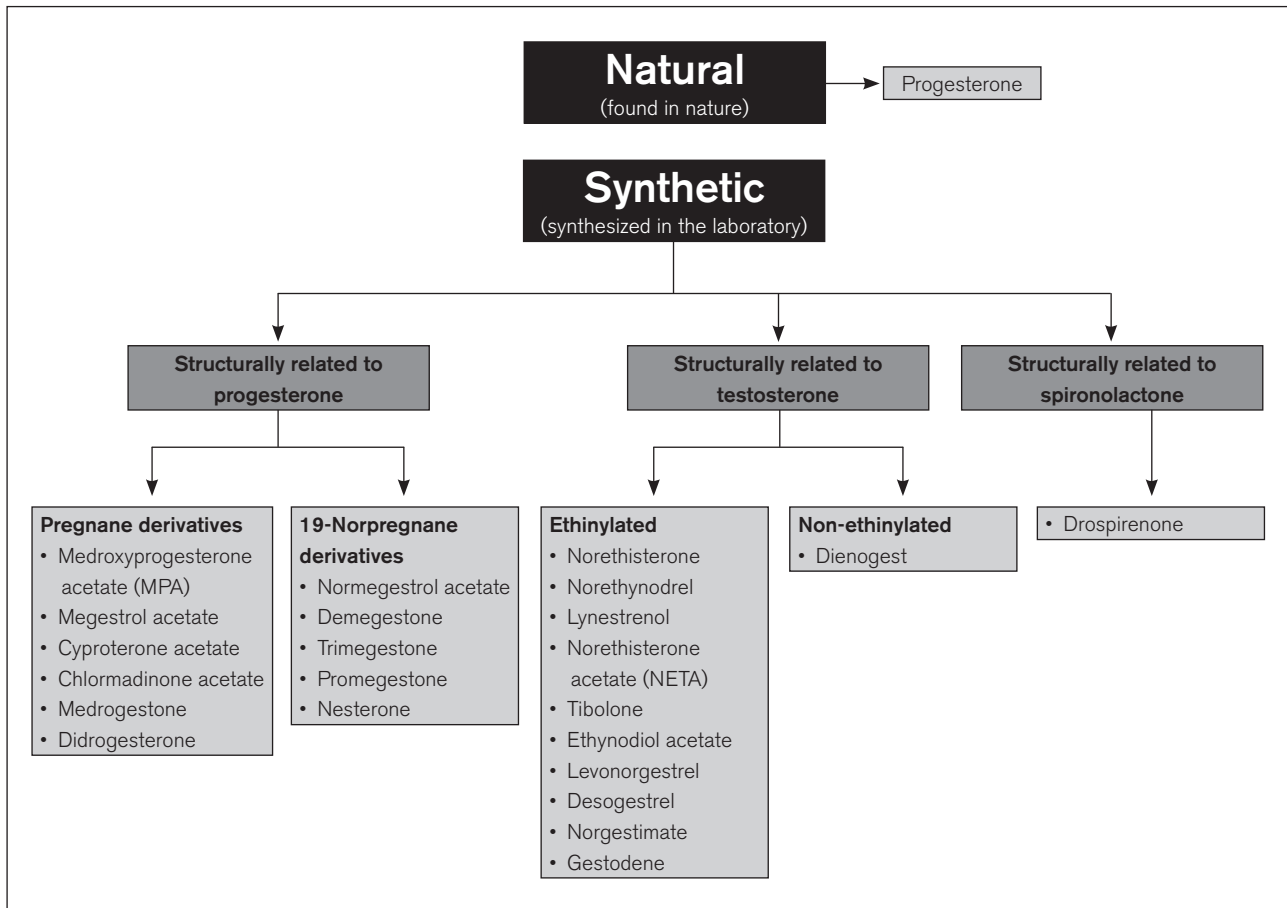
### Progestogens

Use of progestogens is mandatory in patients with intact uterus or in patients submitted to partial hysterectomy with a remainder of endometrial cavity (Class I, Level A).

Even if promotion of secretory activity of a previously estrogen-treated endometrium is mandatory for a progestogen, the specific action on other organs and tissues substantially differ among the different and singular progestogens used in HRT.

Progestogens are obtained through chemical synthesis and the product may be referred to as structurally related to progesterone, testosterone, or spironolactone (Chart 1).

Extra-endometrial action of a progestogen cannot be extrapolated to any other, especially if the molecules are of different pharmacologic origin. Also, it is not possible to talk about class effect of progestogens (especially those related to the atherosclerotic process and CVD) when referring to their non-endometrial action, i.e., the action that a progestogen could have on lipid, lipoprotein, or carbohydrate metabolism, blood coagulation, vasomotricity, and blood pressure. In this sense, some progestogens have specific effects. These may add benefits other than those of the primary endometrial action (which is the objective of its use), whereas other progestogens may impose a higher risk to the user together the endometrial protecting action.



**Chart 1.** Classification of progestogens according to their pharmacologic origin.

For such reasons, progestogens that promote endometrial protection against hyperplasia and cancer and are simultaneously not harmful regarding health and well-being of the HRT user should be used.

Progestogens can also be used with controlled intra-uterine-releasing systems with little or no systemic effects, allowing endometrial protection of patients in estrogen replacement therapy.

### Androgens

Androgen replacement should be indicated for women with clinical signs and symptoms of androgen insufficiency. No treatment with androgens should be given to postmenopausal patients who are not adequately estrogenized.

In bilaterally oophorectomized women or those with adrenal failure, androgen replacement has significant beneficial effects, particularly regarding quality of life and sexual function.

Patients who are on estrogen therapy do not show improvement in hot flashes may benefit from addition of androgens.

For HRT in postmenopausal women, use of androgen

in association with estrogen does not exempt from addition of progestogen for adequate endometrial protection.

When recommended doses are used, the known side effects seem to be infrequent, of little intensity, and completely reversible if identified on time.

Estrogens, progestogens, and androgens may be administered orally or by non-oral routes. The latter comprise the transdermic (hormone-containing adhesives, applied onto the skin), percutaneous (hormone-containing gel, applied onto the skin), vaginal (ovules or creams, indicated only for the treatment of atrophic urogenital manifestations), and nasal (hormone instillation) routes and (biodegradable or non-biodegradable) hormone implants (inserted into the subcutaneous tissue).

Hormone administration by oral and non-oral routes offer different metabolic effects on lipids, lipoproteins, peripheral insulin resistance (Level of Evidence A), and blood coagulation (Level of Evidence B). Because of these diverse actions, it is possible that hormone singularity and administration route influence the atherogenic process and cardiovascular risk.

Regarding HRT risk, it should be recalled that risk for

breast cancer increases in users of combined estrogen-plus-progestogen therapy (Level of Evidence A); however, it is not great in absolute terms, reaching 4 to 6 additional cases of invasive cancer per 10,000/year, only in patients with five or more years of EPT. There is no evidence of breast cancer risk for comparison between continuous and sequential EPT users. On the other hand, there is evidence, limited to a single study (WHI), that isolated estrogen therapy, without progestogen, does not increase breast cancer risk even after a five-year treatment.

The risk of venous thromboembolism (VTE) increases with ET and EPT use, especially in the firsts two years of treatment and in patients over 66 years old (Level of Evidence A). Evidence from observational studies points to a smaller VTE risk with non-oral therapy as compared with oral route (Level of Evidence B).

Estrogen-dependent cancer, acute and recurrent venous thrombosis, porphyria, and acute or severe hepatopathy are the main contraindications to HRT non-elucidated genital bleeding.

There is no scientific reason to impose mandatory obligations regarding HRT duration. Continuation or not of therapy should be decided by the well-informed user together with her health professional, depending on specific goals and an objective estimate regarding risk and benefits besides the possibility of emerging adverse effects.

Patient counseling about HRT risks and benefits should be given in simple terms. Risk data should be expressed in terms of absolute instead of relative numbers. This will allow women and their physicians to take the best decision about HRT.

### **Evidence of hormone therapy influence on cardiovascular disease in climacteric women**

Information on influence of Hormone Therapy on CVD in Climacteric Women was found in Medline-indexed articles after search in the PubMed interface using the following key words: *HRT OR hormone replacement therapy OR hormone therapy AND menopause AND cardiovascular disease*.

The results were limited to the period between 01/01/1990 and 07/04/2007 (date of the search). In addition, the articles were restricted to humans, female gender, English language, and one of the following types of clinical assay, controlled randomized assay, case report, classical article, comparative study, or multicenter study.

The references were first screened by a committee of three physicians who discarded articles without abstract,

reviews, meta analyses, and guidelines and those not related to the objectives of the present study.

The same committee performed a second analysis of the remaining references regarding type of study, objectives, adequate number of participants and studied population, and global quality of the studies; those considered inadequate were also discarded.

These studies were then classified according to the type (randomized, case-control, cohort, etc), objectives, number and characteristics of the population evaluated, hormonal schemes, and main results.

Similarly, the distinct HRT modalities were also grouped regarding their effects on cardiovascular risk markers (such as lipid, lipoprotein, and carbohydrate metabolism, vascular rigidity, atherosclerosis, adhesion molecules, endothelium, vascular inflammatory markers, coagulation, vasomotricity, blood pressure, myocardial or cerebral perfusion, vasodilation, and fat-mass distribution).

Whenever possible, evaluation of time of postmenopause (or at least the patient's age) at HRT start was included in the process of reference selection.

The initial bibliographic search resulted in a total of 574 studies. After undergoing the different levels of selection criteria, 114 publications remained; these suffered an additional in-depth evaluation in order to compose the current knowledge basis and the levels of evidence. After amendments were added to the initial report, the participants invited to the consensus meeting could establish the following conclusions:

1) HRT in women in the period of either menopausal transition or postmenopause is not recommended with the exclusive purpose of reducing CVD risk (Class III, Level of Evidence A).

2) However, there is evidence of a cardiovascular benefit when HTR is started in the menopausal transition or in the first years of postmenopause, also called the window of opportunity (Class IIa, Level of Evidence B) and a cardiovascular risk, when started late (Class III, Level of Evidence B).

3) It should be recalled that use of HRT to alleviate climacteric symptoms of postmenopausal women (Class I, Level of Evidence A) comprises innumerable possibilities of formulation with different estrogens, progestogens, and androgens that can be administered in different therapeutic regimens, hormone associations, doses, and administration routes.

4) There are many evidence gaps regarding HRT regimens used, especially in relation to studies whose final events are clinical outcomes (myocardial infarction, stroke, and thromboembolic events).

5) There are few correctly-delineated clinical stud-

ies analyzing clinical cardiovascular outcomes as the primary objective and HRT modalities studied; in these, use of conjugated equine estrogens (CEE) either alone or in association with medroxyprogesterone acetate (MPA) are predominant.

6) There are specifically delineated studies using estrogen alone or estrogen-progestative therapy with an outcome for CVD in users under 60 years of age.

7) Any of the hormones used in HRT, when alone, has its own and singular effect on the intermediate markers of risk for CVD; however, the effect may vary depending on the association between the hormones used in the therapeutic regimen.

8) Regarding HRT, one cannot speak of a "class effect" on CVD risk. It is recommended that the therapeutic regimen, dose, and administration route be specified.

9) The large amount of existing progestogens used in HRT has different and particular origin, properties, and actions. Since progestogens act on the female body as a whole, their effects on the user's health are beyond the primary objective of endometrial protection, including action on the atherogenic process and cardiovascular risk. Progestogens may interact with different hormone receptors (progesterone, estrogen, androgen glyocorticoid and mineralocorticoid receptors) and each progestogen, with its specific and characteristic actions, will add benefits and risks to the HRT formulated. One cannot indistinctly refer to a class effect of progestogens. Each progestogen has its own and singular effects.

10) There are no studies using testosterone or other androgen in combined therapy with estrogen or an estrogen-progestative formulation.

11) There are no studies on CVD, with an outcome, regarding effects of low-dose therapy of hormone and tibolone.

12) New studies, with correct delineation and well-defined outcomes, specifying the time of postmenopause elapsed, hormone dose, therapeutic formulation, therapeutic regimen of progestogens, and administration routes used, should be performed.

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