Hormonal Replacement and Cardiovascular Disease: a Guideline against the Evidence

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The I Brazilian Guideline for the Prevention of Cardiovascular Diseases in Climacteric Women was recently published in the *Archives*[1]. The initiative is welcome, but it is evident that, even though it is a joint guideline of the Brazilian Society of Cardiology (SBC) and of the Brazilian Society of Climacterium, there is a predominance of colleagues specialized in climacterium among its authors. Only six out 40 participants are cardiologists and practically all of the others are members of the Brazilian Association of Climacterium. Undoubtedly, colleagues that take care of climacteric patients do have expertise in their whole care, but cardiologists surely understand about the prevention of cardiovascular diseases. The lack of isonomy among the specialists who wrote the guideline is inverted at the time of the publication. For now, the publication has been restricted to the *Archives*, a Brazilian leading journal with high visibility. I am unaware of the existence of a journal of the associated specialty and there is no mention of this guideline on the page of the Brazilian Society of Climacterium. I am also unaware of the current rules for guidelines of the SBC, which should include recommendations for carrying out guidelines together with other societies. The formal aspects regarding the publication of this guideline, however, are not the aim of this comment, which intends to challenge, based on the best available evidence, the recommendation for using hormonal replacement therapy (HRT) to prevent cardiovascular disease (CVD) in climacteric women.

Most recommendations from the guideline are universally accepted, applicable to men and women, independently of women being climacteric or not. The main question, however, is the view regarding the indication of HRT aiming at the prevention of CVD. The authors of the guideline affirm that they have searched 574 studies, of which 114 publications were extracted and these were assessed in depth to make up the basis of the knowledge and the available levels of evidence. Based on these publications (which are not specifically cited to substantiate the recommendation), several conclusions have been established by consensus. The statement that there are cardiovascular risks when the HRT is initiated late (Class III, Level of Evidence B), there are no repairs (see below). The conclusion that precedes this statement, i.e., that there is evidence of cardiovascular benefits when the HRT is initiated during the menopausal transition or during the first post-menopausal years (called "window of opportunity") (Class IIa, Level of Evidence B) (literal reproduction of the text, my underlining), is not acceptable and goes against the available evidence. Otherwise, let us see.

Key Words

Cardiovascular diseases / prevention and control; climacteric; menopause; hormone replacement therapy.

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The idea that female hormones are protective against CVD is old and is still deeply rooted. It was drawn from the observation of a lower incidence of CVD in women before menopause, being apparently corroborated by old observational studies. The belief was so strong that estrogens were even administered to men aiming at the secondary prevention of cardiovascular disease. A well-designed clinical trial, the Coronary Drug Project, published in the 70's, abolished that practice, since men treated with estrogens presented a higher incidence of myocardial infarction than recipients of placebo, leading to an early interruption of this arm of the study[2]. The idea that estrogen protects pre-menopausal women has been questioned by the progressive increase in the incidence of coronary heart disease in young women. Probably, the risks to which they are currently exposed, such as the habit of smoking and the competitive professional life, are the real reasons for the loss of the protection, wrongly attributed to the female hormones.

Studies about the putative protection of HRT can be divided as cohort studies, clinical trials with surrogate outcomes and clinical trials with hard outcomes.

More than 20 observational studies were practically homogenous when identifying a lower incidence of CVD among estrogen users. One of the first suggested that even general mortality was lower among women who used HRT[3]. The cohort study with the highest impact was the Nurses' Health Study[4]. This study, which followed 59,337 women for a long period of time, observed a reduction of 40% in the incidence of coronary artery disease (CAD) among HRT users. A meta-analysis of 25 studies showed a relative risk of 0.70 for coronary disease among estrogen users[5].

The evidence from observational studies, however, must be taken as hypothesis generators, since some are confirmed in clinical trials and others are not. Vandenbroucke[6] questioned, as early as in 1991, whether the results of these cohort studies could not be biased by the healthier life style of HRT users[6], the ''healthy cohort effect''. Many confounding variables were controlled in the analysis of those cohorts, but Vandenbroucke called attention to the fact that one, the will to live, was

impossible to control for, and that it could be expressed by reasons not investigated in the cohort studies.

Moving ahead in the hierarchy of evidence, we reach clinical trials. Several have been carried out in this area, but most of them employed surrogate outcomes. The largest of them was the PEPI[7] clinical trial, which allocated 875 post-menopausal women to receive placebo or several associations of hormones. There was an increase in HDL levels and fibrinogen decrease, especially among the patients treated with isolated estrogens. The results of the ILLUMINATE study, in which there was a marked increase in mortality among patients treated with torcetrapib, in spite of increases of more than 60% in HDL levels[8], suggest that HDL is not a good substitute of hard outcomes of CAD. Another well-designed clinical trial with surrogate outcomes, published more recently[9], showed no effect of HRT on the onset of new lesions or the progression of the existing coronary lesions, determined by quantitative angiography. This null effect occurred in spite of the decrease in LDL and increase in HDL levels observed among those treated with hormones.

Randomized clinical trials with primordial outcomes, by definition, the outcomes that are easily understood by patients' themselves[10], such as mortality, myocardial infarction, stroke and others, are the ones that provide more consistent responses for the therapeutic decision-making. There is a small number of consistent studies in this context.

The first was the HERS[11] study, which evaluated the effect of the estrogen-progesterone association in the secondary prevention of cardiovascular disease in post-menopausal women with established coronary disease. Surprisingly, at that time, there was an increase of 52% in the risk of coronary heart disease during the first year of the study in the women treated with HRT, a risk that apparently became diluted during the subsequent years. However, the study follow-up confirmed that the risk persisted with the prolonged use[12]. There was also an important increase in the incidence of venous thromboembolic events, including pulmonary embolism, among the participants treated with HRT. The study was intensely debated and criticized. The criticism that was ultimately consistent concerned the older age of the participants (mean of 67 years) and that the pro-thrombotic effects of the HRT would have exteriorized due to the existence of previous vascular disease. The largest study directed at the assessment of the efficacy of HRT in the primary prevention of CAD and other primary outcomes is known by the acronym WHI[13], even though it is only one of the studies of a major investigation on women's health in the USA (Women's Health Initiative). In total, 8,506 patients were randomized to use 0.625 mg/day of conjugated equine estrogens and 2.5 mg/day of medroxyprogesterone, with 8,102 receiving a placebo. After 5.2 years of follow-up, the incidence of the primary outcome, fatal and non-fatal CAD, was 29% higher among the HRT users (95%CI corresponding to an increase of at least 2% up to an increase of 63%).

In a parallel trial, with conjugated estrogen without progestagens compared to placebo in hysterectomized women, there was no increase in the incidence of CAD and breast cancer, but the incidence of stroke was 39% (95%CI: 10 - 77%) higher in the patients treated with estrogen[14], similarly to what was observed in the study with the association of progestagen.

Other HRT risks must be mentioned. The colleagues who are specialized in climacterium have a legitimate interest and competence to care for the prevention of cardiovascular diseases of their patients. On the other hand, cardiologists also have a commitment with other health issues of their patients. The doubled incidence of venous thromboembolic events and the 26% increase in the incidence of invasive breast carcinoma in patients treated with HRT in the WHI[13] study are substantial reasons to avoid the prolonged use of HRT. There were benefits regarding the prevention of fractures and colorectal cancer, but they were broadly overcome in absolute number by the acknowledged adverse effects. Other analyses of the WHI[15,16] study showed that the HRT, with isolated estrogens or estrogens associated with progestagen, did not have any beneficial effect on the cognitive function or dementia prevention in climacteric patients, with both approaches probably being deleterious.

Regardless of other deleterious and beneficial effects of HRT, scientific societies from several countries have been predominantly against the indication of HRT aiming at the prevention of CVD. The most solid document is certainly the one elaborated and subscribed by 36 Scientific Societies or Official Organs in the USA, which concluded, in 2007, that this therapy is contraindicated for the primary or secondary cardiovascular disease prevention in women, classifying it as a Class III intervention (ineffective and possibly deleterious), based on a level of evidence A[17]. There are several Societies of Gynecology and Menopause among the entities that elaborated or subscribed the document.

The Brazilian guideline that originated this comment[1], indicating HRT for the prevention of CVD during the so-called "window of opportunity", is completely contrary to the commented evidence and the position of the scientific societies from other countries. The authors of the Brazilian guideline justify their position affirming that the commented studies were carried out with equine conjugated estrogens, extracted from the urine of pregnant mares, the classic and worldwide known Premarin®, and not with estradiol, currently employed as transdermal patches. They also questioned the type of progestagen employed, saying that other options, typically being currently commercialized by large pharmaceutical corporations, might have a different effect. The newer hormones, however, have not been tested in randomized clinical trials, with the objective of demonstrating its efficacy in the prevention of CVD. As they reproduce the main biological activity of the older agents, it is difficult to suppose that they have effects that are completely different in this context. The idea of the "window of opportunity" is also defended based on the fact that the patients from the WHI and HERS studies were, on average, elderly. The mean age of the patients in the WHI study was 63 years, but 1/3 was aged between 50 and 59 years. There was no interaction between age and the treatment effect, demonstrating that the latter was not different among younger patients, many of them at the so-called "window of opportunity". Finally, the authors of the guideline stated that the clinical reasoning must take into account not only the evidence collected from

placebo-controlled randomized clinical trials, but also the set of clinical variables and the risk factors presented by the patient. This sophist position certainly cannot deny the evidence of higher quality and the absence of any concrete evidence that supports it.

The presented considerations are sufficiently strong to question the indication of HRT to prevent CVD proposed by the I Brazilian Guideline. Meanwhile the Brazilian Society of Cardiology does not reconsider its official guideline, I understand it is prudent to follow the guidelines of the American Heart Association and of its more than 30 associated societies to reduce the cardiovascular risk in climacteric women.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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