

Prevention of Cardiovascular Diseases in Perimenopausal Women and the Influence of Hormone Replacement Therapy: an Evidence-Based Guideline

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In the position of coordinators/participants of the I Brazilian Guideline for the Prevention of Cardiovascular Diseases in Perimenopausal Women of the journal *Arquivos Brasileiros de Cardiologia*¹ published in the last edition², we read, somewhat perplexed, the point of view exposed in the article “Hormone Replacement and Cardiovascular Disease: a Guideline Against the Evidence”, and we were rather confused about the considerations made by the author to contradict the study conducted by the multidisciplinary group that developed that guideline.

The state of confusion starts with an untruth mentioned in that article². The author states something that is not part of the conclusions of the guideline, namely: “the recommendation of using hormone replacement therapy (HRT) for the prevention of cardiovascular diseases (CVD) in perimenopausal women” (literal reproduction, italicized by us). In its first conclusion, out of twelve, in the chapter “Evidences on the influence of hormone therapy on cardiovascular diseases in perimenopausal women”, textually reproduced here, the guideline says that “HRT is not recommended with the sole purpose of reducing the CVD risk in women in the menopause transition or postmenopausal periods (Class III, Level of Evidence A)”. This conclusion was placed ahead of the others not by chance, but rather, as can be clearly inferred, because of its importance. In other words, and not to leave room for any careless reading, the guideline recommends not to use HRT for the prevention of cardiovascular diseases. In this aspect, consensus was reached between the participants, whether cardiologists or not, who joined in the elaboration of the guideline’s conclusions.

On the other hand, let us proceed to the guideline itself, its composition and motivations.

We understand that the adequate health care of the female population, whether in the preventive or therapeutic setting,

can only be achieved when there exists a convergence of interests between the several medical specialists that take part of women’s health. When the I Brazilian Guideline for the Prevention of Cardiovascular Diseases in Perimenopausal Women was conceived and drawn up, it had two main objectives: to develop a guideline for the prevention of cardiovascular diseases in the female population and, in this context, to clarify the role of postmenopausal hormone replacement therapy.

These objectives could only be achieved if specialists taking global care of women (in Brazil, this is mainly in charge of gynecologists) could congregate side by side with cardiologists and endocrinologists. As such, the development of a guideline in conjunction with other societies, in addition to the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia - SBC), seemed absolutely appropriate.

Thus, the Brazilian Society of Perimenopause (Sociedade Brasileira do Climatério – Sobrac) gathered professionals who took the responsibility for the development of the guideline. According to Sobrac, some points regarding the influence of HRT on the cardiovascular risk in women in this stage of life are still not clear.

Sobrac is a thematic, multiprofessional and multidisciplinary society focused on the study of perimenopause both in women and men. It is not a medical specialty society. Its members are physicians from different specialties, as occurs with other peer societies worldwide, for instance, the International Menopause Society (IMS), the North American Menopause Society, the European Menopause and Andropause Society (EMAS), and others. These international societies also comprise cardiologists, gynecologists, endocrinologists, geriatricians, rheumatologists, breast care specialists, oncologists, etc. Other documents on the same theme that are perfectly in line with our guideline’s conclusions have also been produced by these multidisciplinary societies^{3,4}. Given the importance of these documents, we recommend their reading by all those interested in HRT and CVD.

In view of the reasons given and of the nature of the theme to be addressed – the prevention of cardiovascular diseases in perimenopausal women and the influence of hormone replacement therapy - Sobrac, in partnership with the Brazilian Society of Cardiology (SBC), developed that guideline. In order to form the expert panel that we thought was appropriate for such task, we also invited the Brazilian Society of Endocrinology and Metabolism (Sociedade

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Brasileira de Endocrinologia e Metabologia – SBEM) and the Brazilian Federation of the Associations of Gynecology and Obstetrics (Federação Brasileira das Associações de Ginecologia e Obstetrícia – Febrasgo). The document is divided into two main parts: the first addresses preventive measures and risk stratification in women; the second part provides explanations on the different types of hormones and therapeutic regimens used in HRT, as well as their possible effects on the cardiovascular risk.

The discussion on the theme “postmenopausal HRT” is not closed, nor has the published guideline resolved the pertinent controversies. Much remains to be clarified about this issue, as is also acknowledged in the document elaborated and signed by 36 scientific societies or official agencies in the United States, which, in 2007, pointed to the need for further studies on hormones, so that the way they effectively influence CVD in women could be understood⁵. We would like to seize the opportunity of the mention of this publication to say that it is perfectly in line with the first conclusion of our guideline, when it states that “HRT and selective estrogen-receptor modulators (SERM) should not be used for the primary or the secondary prevention of CVD (class III, level A)”⁵.

We recall that some themes are best discussed when different experts gather together, particularly when there is borderline knowledge that overlaps between different specialties. Today, with the avalanche of knowledge that is available, we cannot disregard this multidisciplinary approach. Xenophobia and sectarianism are repulsive in themselves and absolutely unacceptable in the context of science.

In this sense, there is no doubt that cardiologists are the highest authorities capable of giving opinion on cardiovascular diseases. However, knowledge from other areas also permeates this discussion, as is the case of the diversity of hormones used in HRT; in this sense, endocrinologists and gynecologists could bring important contribution, although the guideline had only addressed the cardiovascular diseases. This observation has also been included in our guideline when it warns, in its conclusions, that each hormone used in HRT has its own and singular effect on the intermediate risk markers of CVD. When the hormone dose is changed or when it is administered in combination with other hormones (combined hormone therapy), the effect previously observed may be different. The guideline also underscores that one should not talk about a “class effect” of HRT on the CVD risk. It is recommended that the therapeutic regimen, the dose and administration route be specified. Therefore, we should remember that the best of evidences obtained regarding the effects of a certain hormone combination used in HRT on the CVD risk in perimenopausal women should not be hastily extrapolated to all other regimens, doses and hormone administration routes. An evidence with a restricted character should not be universalized.

The cardiologists that participated in the development of the guideline, with their reputable credibility, made a major contribution to the conduction of the works and interacted with the other participants in a respectful and harmonious manner. The guideline’s conclusions were always based on the evidences that were discussed, supported by the conviction of the attendees, and devoid of any particular interest or passion.

This was not a nominal voting in which the prevalence of a higher or smaller number of participants from a determined society could influence the final result. Naturally, and for obvious reasons, the opinions of cardiologists carried great weight in the development of the guideline.

As for the other considerations made by the author of the refutation² to the I Brazilian Guideline for the Prevention of Cardiovascular Diseases in Perimenopausal Women¹, and in order to avoid unnecessary repetitions, we recommend the reading of the text of the guideline itself, where all the evidences available at the time of its development - and in which the conclusions are based - are considered in a rational manner.

Incidentally, the 574 articles selected for the initial analysis resulted in a bibliographic research of the scientific papers published and indexed in Medline, at the PubMed website (www.pubmed.com), in the period from January 1st, 1990, to July 4th, 2007 (the date when the research was carried out). The 114 publications that were evaluated more in depth to comprise the current knowledge basis, and the levels of evidence available were previously tabulated and handed out to all participants of the meeting. The fact that not all, but only some of them were mentioned, as is demanded in the refutation article¹, is due to the structure used in the final elaboration of the document, where only the articles that added more relevant contribution were included. Incidentally, this is a quite common practice in similar documents. It was not different with the article that the author of the refutation to the Sobrac and SBC guideline considered the most valuable, and which was used as the basis for his argumentation. Without including all the manuscripts in their bibliographic references, the authors of the said article stated that 154 abstracts on the topics HRT and SERM were identified, of which only 24 were included for in-depth analysis⁵. We should emphasize, however, that the absence of a complete list did by no means decrease the importance of this publication⁵. Furthermore, the word hormones is cited in only three instances in the body of the article⁵; thus, this publication cannot be considered as having explored the theme HRT and CVD adequately and in depth, despite its appropriate recommendation on the issue, as has already been acknowledged.

Dr. Fuchs’s most evident point of disagreement is related to the expression “window of opportunity”. The period of time that includes the first two years after the beginning of menopause is the moment when gynecologists indicate HRT. Even in this phase, HRT is not indicated for cardiovascular prevention. The clinical trials cited by Dr Fuchs – HERS and WHI, that demonstrated increased cardiovascular risk, started HRT most times in patients far beyond this age. In this period, several studies, WHI included, did not show an evident increase in the cardiovascular risk. The risk of venous thrombosis is long known and real, and is mentioned in the package insert of these medications. However, subgroup analyses (which have their methodological limitations) have consistently demonstrated that the risks of infarction are not evident in younger women (less than 10 years after menopause). Meta-analyses of clinical trials demonstrated that HRT reduces mortality in this period of time.

In this line of evidence, Lobo⁶ analyzed two randomized

clinical trials that included 4,065 healthy women with a mean age of 53.6 years. The incidence of cardiovascular events was 1.96 events per 1,000 patients/year in the HRT group and 3.01 events per 1,000 patients/year in the placebo group. These results were observed in a group of patients that is 1.5 times larger than the group of patients with ages between 50 and 60 years in the WHI study. These data corroborate the safety of the prescription of HRT in younger women, and the author concludes that neither does an increased cardiovascular risk nor a possible cardiovascular benefit exist in this age range.

Rossouw et al⁷ carried out a WHI subgroup analysis. Among women aged between 50 and 59 years who were randomized for the use of HRT, there was a non-significant trend of reduction of myocardial infarction and a significant mortality reduction (risk ratio of 0.7 and CI from 0.51 to 0.96). The group of women younger than 55 years could not be stratified. In the age ranges above 60 years, a significant increase of cardiovascular events in the HRT group was observed in relation to the placebo group.

Salpenter et al⁸ carried out a meta-analysis of 23 randomized clinical trials (from 1966 to 2002, with duration of at least 6 months), including 39,049 patients, and showed that HRT significantly reduced events (OR of 0.63 and CI from 0.48 to 0.96) in younger women (less than 60 years old or menopause for less than 10 years), but did not reduce events in the older group. These authors had already carried out

another meta-analysis (2004) which demonstrated a mortality reduction in younger patients using HRT⁹.

As for the choice of the journal in which to publish this guideline, once again we believe we made the right decision. We make ours the words of the author of the refutation to the guideline. The journal *Arquivos Brasileiros de Cardiologia* is a "leading Brazilian periodical with high visibility". Furthermore, we cannot see what other medical journal, in our setting, could be more appropriate for the publication of this guideline. After the publication in *Arquivos*, Sobrac also included the content of the guideline in its website (www.sobrac.org.br) and made it available to all its associates, as can be easily confirmed.

All things considered, we are firmly convinced that the guideline published¹ is in perfect tune with the evidences that were available at the time it was developed, and that it offers a relevant contribution to all those, in our midst, interested in CVD in perimenopausal women. Thus, to the best of our knowledge, we are not able to understand the reasons of the refutation or the label given to the guideline², when considering it contrary to the evidence.

Although the cardiology community may keep the contraindication exclusively for cardiovascular prevention, it is important to point out that HRT should be indicated for women at a low cardiac event risk who can benefit from its use (window of opportunity).

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