

# Blood Pressure, Arterial Function, Structure, and Aging: The Role of Hormonal Replacement Therapy in Postmenopausal Women

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*The occurrence of natural menopause may indicate that a woman is entering a period of increased risk for cardiovascular disease, due to both chronologic aging and lower levels of estrogen. This brief review aims to demonstrate the relevance of changes in blood pressure and large artery structure and function occurring after menopause. These changes, i.e., thickening and stiffening of large arteries (which, in turn would also result in increased systolic and pulse pressures), were found to predict subsequent cardiovascular events, independently of other known cardiovascular risk. The benefits of early hormone replacement therapy on the life expectancy of women have dramatically lost consensus since publication of the Women's Health Initiative study results. However, the authors believe that those results should increase the attention paid by clinicians and public health researchers to the individualization of hormone replacement therapy prescription for postmenopausal women, and to a better characterization of those vascular parameters and profiles identifying postmenopausal women who are most likely to benefit from specific hormone replacement therapy in terms of cardiovascular protection. (J Clin Hypertens. 2003;5:219–225) ©2003 Le Jacq Communications, Inc.*

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A 2001 statement from the American Heart Association<sup>1</sup> recommended that hormone replacement therapy (HRT) should not be used for secondary prevention of cardiovascular disease (CVD). Later, the July 17, 2002 issue of *JAMA* presented the results from the Women's Health Initiative (WHI) study.<sup>2</sup> The strength of the WHI study findings, supported by the rigorous design, the large sample size, and the long follow-up, appears to have put the word "end" to the use of HRT for prevention of CVD in postmenopausal women.

We have neither the authority nor clear evidence to provide an alternative approach to the statement reported in the paper by the WHI study investigators. However, as noted in an editorial relating to the WHI Study,<sup>3</sup> 46 million prescriptions for conjugated estrogens (Premarin) were written in the United States in 2000. The idea that so many doctors prescribed an "inappropriate" treatment for so many years is difficult to accept.

For example, increasing attention should be paid to exploring criteria that could be used for a greater individualization of HRT prescriptions for postmenopausal women and better-characterized risk factor profiles that would identify postmenopausal women who are most likely to benefit from specific HRT in terms of cardiovascular protection.

The results of this clinical trial are certainly true for oral HRT administration, but current clinical practices are often based on transdermal administration. Some preliminary data suggest that the two treatment approaches may not be equivalent.

The goal of the present manuscript is to very briefly underline some issues still to be addressed with regard to the effects of HRT on large artery

structure and function and, thus, on the individual risk of cardiovascular events.

### WOMEN'S AGING AND CVD

The widening of the gender differential in life expectancy has been a central feature of mortality trends during the 20th century. In 1900, the European/North American gender gap in life expectancy was typically 2–3 years. Currently, women in most developed countries outlive men by 6–8 years. It is commonly believed that one of the main factors accounting for the longer life expectancy in women is the natural protection against CVD conferred to women by cyclical endogenous ovarian hormonal production before menopause. Indeed, after menopause, the risk of CVD in women increases substantially.<sup>4</sup> However, men experience higher rates of cardiovascular events at all ages. When the comparison is limited to persons affected by hypertension, the age-specific rates of stroke, left ventricular hypertrophy, and renal failure are similar in the two sexes. This, in part, may explain one of the important paradoxes in geriatric research, i.e., although women have a longer life expectancy than men, they live a greater number of years with disabilities.

Stroke is the leading cause of disability in the developed world.<sup>5</sup> Worldwide, approximately 20%–30% of stroke survivors suffer major disabilities, and only 50%–75% are able to walk unaided.<sup>6</sup> An increased blood pressure (BP) level is probably the most important risk factor for stroke; this therefore, is particularly important in women because BP is modifiable. Thus, appropriate treatment of high BP may lower the disparity between men and women in the quality of late life.

### BP, ARTERIAL STRUCTURE AND FUNCTION, AGING, AND MENOPAUSAL TRANSITION

Gender differences in BP are detectable during adolescence and persist through adulthood.<sup>7</sup> In all racial groups, young and middle-aged men tend to have higher systolic and diastolic BP (SBP/DBP) than women of similar age. Thus, through middle age the prevalence of hypertension is higher among men than women. The Third National Health and Nutrition Examination Survey (NHANES III)<sup>8</sup> pointed out that after the sixth decade hypertension becomes more prevalent in women than in men. SBP is higher in men than in women until the age of 50 years for blacks and for whites until the age of 65 years; thereafter, it becomes higher in women.<sup>9</sup> Although, in general, postmenopausal women have higher BP values than premenopausal women, the age-related increase in BP in women becomes steeper after the age of 62 years,

suggesting that the decrease in the levels of serum estrogen levels may not be the primary and/or the unique cause.<sup>8</sup>

Arterial stiffening is thought to play a role in the etiology of hypertension,<sup>10</sup> although the temporal association between arterial stiffness and increased BP levels in humans requires further elucidation. Increased arterial stiffness has been found to be associated with a number of cardiovascular risk factors, including age, male sex, hypertension, lipoprotein abnormalities, and diabetes.<sup>11</sup> It has been established that pulse pressure, a surrogate measure of arterial stiffness, is an independent predictor of future cardiovascular events.<sup>12–14</sup>

Arterial stiffness, as determined by aortofemoral pulse wave velocity (PWV), increases with age in both sexes. Aortofemoral PWV doubles between ages 18–80 years.<sup>15</sup> A study<sup>16</sup> in 600 normotensive subjects has indicated that arterial compliance in premenopausal women is greater than that in men of equivalent age, but this gender difference is lost after menopause; this suggests that arterial compliance declines rapidly after menopause.

Arterial stiffness may also be affected by the vessel structure; indeed, the Moens-Korteweg equation suggests that PWV is related to arterial wall thickness. Common carotid artery intima-media thickness (IMT) is an index of arterial wall thickness commonly used in epidemiologic studies and clinical trials. This can be measured accurately, reproducibly, and noninvasively by ultrasound. In the Atherosclerosis Risk in Communities (ARIC) study, among women aged 45–54 years, the mean IMT was 0.65 mm for premenopausal women and 0.75 mm for those who had been postmenopausal for 5 years and more.<sup>17</sup>

### EFFECTS OF HRT ON VASCULAR AGING, BP, ARTERIAL STIFFNESS, AND THICKNESS IN POSTMENOPAUSAL WOMEN

The reasons for gender differences in BP are not known. It has been suggested, but not proven, that estrogen is responsible for the lower BP in younger women. The influence of menopause on BP is also controversial. Cross-sectional studies have reported significantly higher SBP and DBP in postmenopausal than in premenopausal women,<sup>18–20</sup> even after adjusting for age. Nevertheless, longitudinal studies have not documented an accelerated increase in BP following menopause.<sup>21,22</sup> Staessen and colleagues<sup>18</sup> reported a four-fold higher prevalence of hypertension in postmenopausal than in premenopausal women. After adjustment for age and body mass index, postmenopausal women

were still more than twice as likely to have hypertension as premenopausal women. Diabetes and dyslipidemia are also more prevalent in postmenopausal than premenopausal women.<sup>23</sup>

Whether reduced ovarian estrogen production plays a major role in the increase in BP after menopause is unclear. An association between HRT and hypertension in postmenopausal women was reported in the 1970s and 1980s and influenced many physicians to consider elevated BP levels as a contraindication of HRT prescription. However, most cross-sectional studies have found no net effect of HRT on BP<sup>18,24,25</sup> and it has been suggested that HRT may even lower BP.<sup>26</sup> The formulation and site of administration of HRT may also be important in determining the type and magnitude of BP response.<sup>27</sup> In a cross-sectional study, we recently observed that in postmenopausal HRT users SBP was lower than in women nonusers.<sup>28</sup>

Many of the observational studies mentioned above have important limitations in their design and conduct, which may limit the generalizability of the findings: i.e., lack of randomization of treatment or placebo control, small sample size, and pooling of data from women treated with a variety of different estrogens (natural, conjugated equine, semisynthetic, administered orally or parenterally), and/or progestins—combinations collectively defined as HRT.

Longitudinal studies on the effect of HRT on BP are scarce. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial<sup>29</sup> evaluated cardiovascular risk factors in 875 normotensive postmenopausal women aged 45–64 years, randomly assigned to treatment with a variety of HRT regimens. After 3 years of follow-up, there were no differences in SBP or DBP in any of the treatment groups compared to placebo, although a gradual increase in SBP with aging was observed, regardless of the presence or absence of HRT. In a longitudinal study, we recently found that postmenopausal women on HRT have a lesser rise in SBP over time than those not on HRT, whereas HRT does not affect longitudinal changes in DBP.<sup>30</sup> Possible explanations for the difference between the PEPI results and our findings may be the older age and the longer follow-up time of the participants in our study. Of note, neither of the two large randomized trials on HRT and secondary prevention of CVD—the Heart and Estrogen/Progestin Replacement Study (HERS)<sup>31</sup> and the Estrogen Replacement in Atherosclerosis (ERA) trial<sup>32</sup>—included BP among the measured variables. A similar limitation is present in the large observational Nurses' Health

Study,<sup>33</sup> which included more than 70,000 postmenopausal women. The limitations of the conclusions of currently available observational longitudinal studies on the benefit of HRT in prevention of coronary disease in postmenopausal women have been discussed in a recent editorial.<sup>34</sup>

BP levels are positively associated with arterial stiffness and thickness. Independently of the effects of HRT on BP, several studies have focused on the effects of HRT on arterial stiffness and/or thickness of postmenopausal women.

#### EFFECT OF HRT ON ARTERIAL COMPLIANCE AND VESSEL THICKNESS

With regard to the long-term effects of HRT on arterial stiffness, Rajkumar et al.<sup>35</sup> found that postmenopausal women 50–70 years of age treated for an average of 6.7 years underwent a significant reduction of aortofemoral PWV and an increase in systemic arterial compliance compared to age-matched controls not on HRT. Those women on estrogen alone showed similar beneficial effects to those on a combination of estrogen plus progestin. McGrath et al.<sup>36</sup> described a protective effect of long-term estrogen replacement therapy on age-related changes in systemic arterial compliance and in carotid distensibility, in both smokers and nonsmokers among postmenopausal women. Progestin reduced the beneficial effect on carotid distensibility, but not on systemic arterial compliance.

In the Cardiovascular Heart Study (CHS), among women aged 65 years and older, the mean IMT was thinner with both current estrogen-progestin and current estrogen replacement therapy than in controls.<sup>37</sup> These findings were later confirmed in the Rotterdam Study.<sup>38</sup> Another cross-sectional study confirmed this finding both in smokers and nonsmokers among postmenopausal women on HRT for at least one year.<sup>36</sup> In the Asymptomatic Carotid Atherosclerosis Progression Study (ACAPS), HRT has been reported to reduce or halt the progression of IMT.<sup>39</sup>

An overview of the major findings of the literature concerning the effects of HRT on BP, arterial stiffness, and thickness is given in the Table.

#### POTENTIAL MECHANISMS

Regardless of potential limitations in the study design discussed above, the beneficial effects of HRT on arterial function and structure were initially ascribed to a better lipid profile in postmenopausal women using HRT.<sup>40</sup> Hemodynamic changes may differ for short-term and long-term HRT administration. For instance, echocardiographic studies have suggested either no

<b>Table.</b> Effects of HRT on Blood Pressure (BP) and Arterial Stiffness and Structure			
STUDY	HRT REGIMEN	DESIGN	EFFECT
<b>EFFECTS OF HRT ON BP</b>			
Lind et al. <sup>26</sup>	Estrogen	Placebo	Reduction in SBP and DBP
PEPI Trial <sup>29</sup>	Estrogen	Placebo	No changes in BP
Seeley et al. <sup>19</sup>	Estrogen	Placebo Crossover	Reduction in SBP and DBP*
Lind et al. <sup>26</sup>	Estrogen + progestin	Placebo	Reduction in SBP and DBP
PEPI Trial <sup>29</sup>	Estrogen + progestin	Placebo	No changes in BP
Seeley et al. <sup>19</sup>	Estrogen + progestin	Placebo Crossover	Reduction in SBP and DBP*
Scuteri et al. <sup>30</sup>	Estrogen + progestin	Longitudinal	Reduction in SBP increase over time
<b>EFFECTS OF HRT ON ARTERIAL STIFFNESS</b>			
Rajkumar et al. <sup>35</sup>	Estrogen	Placebo	Reduced PWV and increased SAC
McGrath et al. <sup>36</sup>	Estrogen	Case-control	Higher SAC
McGrath et al. <sup>36</sup>	Estrogen + progestin	Case-control	Higher SAC than controls. No difference in SAC vs. estrogen alone, lower carotid DC than estrogen alone
<b>EFFECTS OF HRT ON ARTERIAL STRUCTURE</b>			
McGrath et al. <sup>36</sup>	Estrogen	Case-control	Decrease in common carotid IMT
Jonas et al. <sup>37</sup>	Estrogen	Cohort Cross-sectional	Decrease in common and internal carotid arteries IMT
McGrath et al. <sup>36</sup>	Estrogen + progestin	Case-control	Decreased IMT compared to controls. No difference vs. estrogen alone
Jonas et al. <sup>37</sup>	Estrogen + progestin	Cohort Cross-sectional	Decrease in common and internal carotid IMT compared to controls, similar to estrogen alone
Westendorp et al. <sup>38</sup>	HRT	Cohort Cross-sectional	Decrease in common carotid IMT
Espeland et al. <sup>39</sup>	HRT	Placebo Longitudinal	Halted progression of IMT
HRT=hormone replacement therapy; SBP/DBP=systolic/diastolic blood pressure; PWV=pulse wave velocity; SAC=systemic arterial compliance; DC=distensibility coefficient; IMT=intima-media thickness; *24-hour ambulatory BP measurements			

effect of estrogen replacement therapy on cardiac function<sup>41</sup> or a positive inotropic effect,<sup>42</sup> which would tend to increase rather than reduce SBP. More recently, a study using invasive left ventricular and aortic function evaluation found that acute estrogen administration did not change left ventricular ejection fraction or ejection time.<sup>43</sup> Although changes in vascular loading conditions may underlie the short-term effects of estrogen

on arterial compliance, long-term effects may be mediated by structural vascular changes.

More recently, evidence has emerged supporting the idea that the positive effects of estrogen are mediated by vascular-derived (endothelial and nonendothelial) factors.<sup>44,45</sup> A second hypothesis suggests that long-term HRT exerts its effects on arterial BP and stiffness via structural changes in the vasculature, although this

mechanism remains speculative. Arterial stiffness, for which SBP is a reasonable surrogate, is determined by the relative amount of distensible tissue such as smooth muscle and elastin and less distensible collagen fibers in the vessel wall. Fragmentation of elastin and a progressive increase in the number of collagen fibers, a common feature of aging, result in increased stiffness of large arteries and higher SBP. Structural changes in the arterial wall may represent a mechanism through which HRT exerts its effects on arterial stiffness and SBP. In support of this concept, previous studies in experimental animals showed that estrogens can modulate the relative proportion of collagen and elastin (i.e., reduction of collagen accumulation and of elastin loss)<sup>46</sup> and reduce smooth muscle cell proliferation.<sup>47</sup> Increased nitric oxide production may represent an additional mechanism by which HRT may slow down the change in SBP over time. HRT has been shown to increase endothelial-dependent vasodilation and to increase plasma levels of nitrite/nitrate.<sup>48,49</sup>

### ESTROGENS:PROGESTINS

A major unanswered question in HRT for postmenopausal women is how to balance estrogen with progestin. Use of unopposed estrogen has been thought to increase the risk of breast and endometrial cancer; this risk may be lessened by continuous or cyclic addition of a progestin.<sup>50</sup>

Although synthetic and natural progestins are generally viewed as equivalent, animal studies<sup>51,52</sup> have found that when they are combined with estrogen, their vascular effects may differ. For instance, medroxyprogesterone acetate was found to antagonize the beneficial effects of estrogen on connective tissue changes (i.e., reduction of collagen accumulation and elastin loss) in aortas from monkeys fed an atherosclerotic diet.<sup>53</sup> This experimental observation may be consistent with the clinical observation of greater arterial stiffness (assessed as PWV) in postmenopausal women with SBP >130 mm Hg, a level typically exceeded by postmenopausal women.<sup>28</sup> The potential pressor effects of progestins, possibly through an increase in plasma renin activity, may offset any potential beneficial effect of estrogen on vascular tone.

### Types of Estrogens and Progestins

Participants in both the WHI study for primary prevention and the HERS study for secondary prevention were given medroxyprogesterone acetate as progestin. To further support the relevance of this issue, "WHI is testing the hypothesis of whether oral estrogen will prevent coronary heart disease in 10,739 women who have had a hysterectomy. The monitoring of this trial

is similar to that for the trial of estrogen plus progestin. At an average follow-up of 5.2 years, the data and safety monitoring board has recommended that this trial continue because the balance of overall risks and benefits remains uncertain. These results are expected to be available in 2005, at the planned termination."<sup>2</sup>

### Age of Initiation of HRT

There are no analyses noting the effects of HRT on cardiovascular risk as a function of the onset age of initiation of replacement therapy. Both the study population of the WHI study, for primary prevention, and of the HERS study, for secondary prevention, include women in a wide age range. If the natural course of a woman's life is to lose exposure to sex steroids after menopause, it is hard to believe that the cardiovascular effects of HRT may be similar in early menopause, i.e., in the 50s, as in the 70s.

Furthermore, hemodynamic effects may differ for short-term and long-term HRT administration. For instance, whether inotropic effects observed after short-term HRT administration<sup>42</sup> differ in younger and older women has not been demonstrated. In addition, it has not been addressed whether the short-term cardiac effects of HRT described above may somehow be responsible for the observation that the difference between treatment groups in coronary heart disease hazards is apparent soon after randomization.<sup>2,31</sup>

### Dose-Response

The Writing Group for the WHI<sup>2</sup> acknowledged that the results from the WHI study do not necessarily apply to lower dosages of HRT, either estrogen or progestin or both. Indeed, results from the Nurses' Health Study had already reported no increase in the apparent benefit of HRT with increasing doses of estrogen.<sup>54</sup> Although a dose response is clearly observed for the beneficial effects of estrogen on lipids,<sup>54</sup> higher doses of estrogen also increase the risk of cancer. With regard to the dose-response of HRT on BP, a 1999 observation in normotensive postmenopausal women found that transdermal estradiol at a physiologic dose of 50 µg/day—corresponding to plasma levels detectable during the mid-follicular phase menstrual cycle—resulted in a significant decrease in nocturnal BP with restoration of a more physiologic nocturnal rhythm of BP.<sup>20</sup>

### Oral vs. Transdermal

Most women in studies of estrogen replacement therapy and CVD took estrogen orally. Little evidence has been provided on whether transdermal

estradiol has similar effects. As acknowledged by the WHI Study, "it remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile."<sup>2</sup>

## CONCLUSION

The occurrence of natural menopause may indicate that a woman is entering a period of increased risk for CVD, due to both chronologic aging and lower levels of estrogen. This brief review highlighted some of the changes in blood pressure and large artery structure and function occurring after menopause. These changes, i.e., thickening and stiffening of large arteries (which, in turn also results in increased systolic and pulse pressure), were found to predict subsequent cardiovascular events, independently of other known cardiovascular risk.

We believe that the first years after menopause should become a prime period for implementing clear strategies aimed at preventing future disease and disability. This early prevention strategy, if effective, would have an impact similar to that observed in the past with vaccination against infectious disease in infants. The beliefs about early HRT on the life expectancy of women have changed since publication of WHI Study results.<sup>2</sup> We believe that those results should increase the attention of clinicians and public health researchers toward the individualization of HRT prescriptions for postmenopausal women. A better characterization of those vascular parameters in postmenopausal women who are most likely to benefit from specific HRT in terms of cardiovascular protection is necessary. Furthermore, the finding of the WHI Study shows that more research in this field is needed.

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