Date of release: 17 November, 2014

Postmenopausal hormone therapy and blood pressure revisited

The effects of hormone therapy (HT) on mean and visit-to-visit variability (VVV) of blood pressure in postmenopausal women were recorded in the Women's Health Initiative (WHI) randomized controlled trials [1]. Blood pressure was measured at baseline and annually in the two WHI HT trials, in which 10,739 and 16,608 postmenopausal women were randomized to conjugated equine estrogens (CEE, 0.625 mg/day) or placebo, and CEE plus medroxyprogesterone acetate (MPA, 2.5 mg/day) or placebo, respectively. At the first annual visit (year 1), the mean systolic blood pressure was 1.04 mmHg (95% confidence interval (CI) 0.58–1.50) and 1.35 mmHg (95% CI 0.99–1.72) higher in the CEE and CEE + MPA arms, respectively, compared with the mean systolic blood pressure in women taking the corresponding placebos. These effects remained stable after year 1. CEE also increased the VVV of systolic blood pressure (ratio of VVV in CEE vs. placebo, 1.03; $p < 0.001$), whereas CEE + MPA did not (ratio of VVV in CEE + MPA vs. placebo, 1.01; $p = 0.20$). After accounting for study drug adherence, the effects of CEE and CEE + MPA on mean systolic blood pressure increased at year 1, and the differences in the CEE and CEE + MPA arms vs. placebos also continued to increase after year 1. Further, both CEE and CEE + MPA significantly increased the VVV of systolic blood pressure (ratio of VVV in CEE vs. placebo, 1.04; $p < 0.001$; ratio of VVV in CEE + MPA vs. placebo, 1.05; $p < 0.001$).

Comment

It is well documented that elevated blood pressure in women is an important risk factor for cardiovascular disease and therefore its control may have a substantial impact on women's health [2,3]. Shimbo and colleagues [1] concluded that, in the particular clinical set-up of the WHI trial (women at a mean age of 62 years using CEE or CEE + MPA at conventional doses), mean and VVV of systolic blood pressure were increased. Thus, these results actually support the WHI-related notion that HT may have a detrimental effect on coronary artery disease. Although the exact mechanisms that may explain how HT influences blood pressure are not fully understood, several possibilities have been suggested [4]. HT has an effect on vascular tone, cardiac function, the immune system, the kidneys and other organs. Of particular interest is the modulation of the renin–angiotensin pathway by estrogen.

Years ago, the Nurses' Health Study (healthy females, aged 30–55 years, long follow-up) demonstrated an impressive protective effect of HT on the heart, which was not altered after adjustment for various cardiac risk factors, including hypertension [5]. The PEPI randomized, placebo-controlled trial back in the mid-1990s (healthy

postmenopausal women, aged 45–64 years) demonstrated a slight elevation in systolic blood pressure in all study arms (HT and placebo) during the 3-year follow-up; this elevation was related to aging rather than to hormone use [6]. Furthermore, a review by Coylewright and colleagues on hypertension in women examined possible associations with menopause *per se* [7]. Because of conflicting findings in various studies and cohorts, which led to heavy debates, a clear-cut conclusion could not be reached. Thus the review ended with a cautious phrasing: 'Menopausal effects appear to be small and may be masked by age-related changes that increase blood pressure'.

Later on, the neutral effect of menopause on blood pressure on the one hand and that of HT on the other hand excluded hypertension from the list of research priorities vis-a-vis potential interactions between these three parameters. However, the issue was brought back to the table when Angeliq was approved and the property of its constituent drospirenone to lower blood pressure was presented as an innovation in the field of HT [8]. Yet, results from the '45 and up' observational study on healthy aging in a large Australian cohort did find an increased risk of hypertension in all age groups in current or past hormone users [9]. Of 43,405 postmenopausal women with an intact uterus who did not have hypertension at baseline, 12,443 were exposed to HT and 2536 developed high blood pressure. The adjusted odds ratios (OR) for past HT use according to age were reported to be: < 56 years, OR 1.59 (99% CI 1.15–2.20); 56–61 years, OR 1.58 (99% CI 1.31–1.90); 62–70 years, OR 1.26 (99% CI 1.10–1.44). Increased duration of hormone use was associated with higher odds of having high blood pressure, with the effect of HT use diminishing with increasing age. Following the publication of this study, Shapiro and Pines challenged the significance of its results based on several potential defects and biases in methodology [10].

In recent years, no further significant data on blood pressure and menopause-related issues have been published. This is reflected in a 2014 review of the literature, pointing again at controversies and conflicting evidence [11]. This uneventful period has now been interrupted in 2014 by several important pieces of new information. The first one is the WHI study already detailed above [1]. The second is a release from the KEEPS study, which was aimed at healthy, early postmenopausal women who took oral or transdermal HT for 4 years [12]. No differences in blood pressure between the 0.45 mg/day oral CEE, the 50 µg/day transdermal estradiol and the placebo arms were recorded. To note, both HT groups received 200 mg progesterone for 12 days every month as well. Thus, the bottom line is that there is no clear-cut evidence from randomized studies to support an association between blood pressure and HT. The WHI and KEEPS cohorts were very different in their basic characteristics: in the WHI study [1], women started HT at a mean 10 years after entering menopause, and the mean increase in blood pressure during HT (oral CEE at standard

doses) was in the order of 1 mmHg. Contrarily, the KEEPS study enrolled younger women who had just became menopausal and were prescribed lower doses of HT, including by a transdermal route [12]. These women did not demonstrate an increased risk for an adverse change in blood pressure. Perhaps additional good-quality studies with longer follow-up periods will allow better understanding of this issue.

By the end of the day, whether there is or there is not a small ill effect of estrogen deficiency (menopause) or estrogen replacement (HT) on blood pressure seems secondary to the importance of monitoring and optimal control of blood pressure in midlife women to reduce the risk for future cardiovascular events.

Amos Pines
Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel