27.1 Introduction

In 2008, the World Health Organization global status report estimated that 7.5 million deaths were attributed to high blood pressure (BP) [1]. High BP is responsible for 54% of stroke and 47% of ischemic heart disease cases. Overall, 80% of the disease burden attributable to Hypertension occurred in low-income and middle-income economies, and over half in people aged 45–69 years [2]. While the prevalence of hypertension clearly increases with age in both genders (www.cdc.gov/bloodpressure/facts.htm), a comparison of cohorts from the third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) with NHANES IV (1999–2002) reveals the proportion of hypertensive individuals to have decreased among men but increased among women over the time period from 1994 to 2002 [3]. Women are about as likely as men to develop high BP during their lifetime.

Although the condition affects more men than women in individuals under the age of 45 years, the age-related increase in BP accelerates in women around the menopause and this gender difference reverses after 45–55 years [4] (www.cdc.gov/nchs/data/hus/hus08.pdf), see Figs. 27.1a, 27.1b. Therefore, although the proportion of women with hypertension (elevated BP or on antihypertensive drugs) below the age of 45 years is one-third to one half to that of men,
numbers become identical in both genders in the 45–54 years age group and then increase further in women after the age of 65 years (Figs. 27.1a, 27.1b). Specifically, the proportions for women are 55 % at 55–64 years, 71 % at 65–74 years, and 80 % above the age of 80 years [4]. This pattern raises the possibility of differing pathophysiologies for hypertension in the two genders and a potential protective effect of sex steroids on the vascular system that is lost after the menopause.

The lower incidence of hypertension in premenopausal women and the increase in incidence following the menopause point to a gender-specific pathophysiology for postmenopausal hypertension. Vasodilation has been observed with fluctuating estrogen levels across the menstrual cycle, pregnancy, or \( 17\beta \)-estradiol supplementation [5–7], and in men after long-term estrogen administration [6]. Vasodilation has also been shown to increase during the luteal phase of the menstrual cycle and during pregnancy, at which time both estradiol and progesterone levels are higher. Endogenous progesterone has been shown to have a vasodilatory and diuretic effect in premenopausal women [8]. The substantial decrease in these endogenous vasodilators at the menopause may unmask a genetic predisposition to hypertension. In addition, menopause is associated with anthropometric, metabolic, and additional hormonal changes. These include weight gain, activation of the sympathetic nervous...
system, alterations in the renin–angiotensin–aldosterone system (RAAS) and endothelin system, and an increased prevalence of metabolic syndrome, all of which may predispose to the development of hypertension [9–11].

In this chapter, we briefly review the potential mechanisms and modulators for the effect of hormone replacement therapy (HRT) on BP, detail its impact on BP in normotensive and then in hypertensive women, underscoring the results from major clinical trials in postmenopausal women.

27.2 Methodology for the Literature Review

A systematic review of the existing literature was implemented, and the topic of interest was divided into three main concepts: hypertension, hormone replacement therapy, and menopause. Each of these concepts was then searched on OVID Medline (www.ovid.com/site/catalog/DataBase/901.jsp) and also as synonyms or related terms to achieve a comprehensive literature review. The OVID Medline interface was used including MeSH terms, explode functions, keyword searching in title, abstract, and subject headings, adjacency, and publication types, in addition to using the AND and OR Boolean operators, and term truncation, to identify all relevant articles using the main terms and related terms. MeSH is used by the indexers at National Library of Medicine to describe the content of an article. These MeSH terms are also organized in a hierarchy or tree structure, and this allows users to explode a MeSH term to ensure that narrower MeSH terms are also included in the search results. The OVID Medline search was conducted from 2000–December 2011. Additional relevant studies and reviews before 2000 and those detailed in the papers retrieved and available in the authors’ libraries were also used.

27.3 Effects of Estrogen and Progesterone on the Cardiovascular System

The effect of estrogen on the cardiovascular system can be through genomic and non genomic mechanisms and is mediated through two receptor isoforms, estrogen receptor (ER) alpha and ER beta [12], and a newly discovered seven transmembrane-spanning intracellular G-protein coupled estrogen receptor (GPER), that is expressed throughout the cardiovascular system [13]. The beneficial effect of estrogen on the cardiovascular system has been suggested in multiple studies evaluating different parameters. The effect on menopause-associated endothelial dysfunction has not been consistent across studies [9]. Similarly, estrogen’s effect on the reinstitute renin angiotensin aldosterone system (RAAS) is complex and involves both stimulatory and inhibitory actions [14]. The increasing activity of the kinin–kallikrein [15] and sympathetic systems [16], an increase in atrial natriuretic
peptide, a reduction in oxidative stress [17] and inflammation [18], are all effects attributed to estrogen, which can result in BP lowering.

Furthermore, estrogen can play an important role on hypertension-associated complications. It has been shown that it can improve left ventricular function and mass [19, 20] and that it can induce a reduction in albuminuria [21], although the studies addressing this yielded differing results [22–24].

Progestins exist in different classes and differ in their metabolic, androgenic, glucocorticoid, and antimineralocorticoid effects. Medroxyprogesterone acetate (MPA), the most commonly used progestin in studies evaluating the impact of HT on cardiovascular outcomes, has been shown to attenuate estrogen’s augmentation of endothelial-dependent vasodilation [25]. Drosperinone is a novel progesterone and spironolactone derivative with antimineralocorticoid and antiandrogenic activity [26]. The studies evaluating the combination of drosperinone and estradiol in hypertensive women showed a significant decrease in blood pressure [27, 28]. However, drosperinone has been associated with an increased risk of venous thromboembolism [29]. Additionally, dydrogesterone, which has minimal or absent effects mediated by receptors other than that of progesterone and a neutral activity on the glucocorticoid, androgenic, and aldosterone receptors [26], was shown to decrease BP when combined to estradiol in healthy and hypertensive postmenopausal women [30, 31].

27.4 Blood Pressure Changes Across the Menopause

A decline in estradiol levels is the cardinal hormonal marker of the menopause transition. Postmenopausal women have a distinctive pattern of blunted day–night BP reduction or nondipping [32] and certain ER polymorphisms have been associated with BP elevation in women [33]. The menopause transition is also characterized by significant changes in body composition, including increments in weight and fat mass [34], and a higher prevalence of metabolic syndrome, conditions associated with inflammation and an increased risk of hypertension [35, 36]. Studies evaluating the relationship between the menopause and hypertension yielded conflicting results, and an assessment of the role of sex hormones in this relationship is quite complex. The conflicting results could in part be explained by differences in study designs, the methods used to measure BP, office BP versus 24-h ambulatory BP monitoring (ABPM), the sample size used, the type of menopause (surgical vs. natural), and patients characteristics such as age, body mass index (BMI), years since the menopause, and general health status. Although there is a good correlation between ABPM and clinic measurements, provided a mean of three measurements is used, the power of ABPM to detect small changes in BP is higher, especially when small sample sizes are used [37]. In many studies, often a single BP measurement was taken, and it has been shown that office BP has a limited relationship with 24-h ABPM and that ABPM is a better predictor of end-organ damage and response to therapy [38].
An acceleration in age-related vascular stiffness in the large vessels occurs at menopause, as was shown in a study where the slope of the 24-h pulse pressure versus age was steeper in menopausal ($n = 149$) women than their premenopausal counterparts ($n = 166$), measured at 0.428 versus $-0.066$ mmHg per year ($p = 0.003$), and male controls ($n = 315$) 0.428 versus 0.188 mmHg per year ($p = 0.06$) [39].

In a 16-year longitudinal study of 408 premenopausal and 160 postmenopausal women, investigators were unable to demonstrate any difference in BP between the two study groups in age-adjusted analyses [40]. In a large cross-sectional epidemiological study evaluating the prevalence of hypertension across menopausal women in an Italian population [Study on Hypertension Prevalence in Menopause in the Italian population (SIMONA)], a significant increase in both systolic BP (SBP) and diastolic BP (DBP) (3.4 and 3.1 mmHg, respectively) was found in more than 18,000 Italian postmenopausal women, aged 46–59 years, compared to premenopausal and perimenopausal women. This finding was independent of age, BMI, smoking status, contraception, and HRT use [41], but was only evident for the younger end of the age range.

Finally, the Study of Women’s Health Across the Nation (SWAN) is a multi-ethnic, community-based, longitudinal cohort study of the natural history of the menopause transition in 3,302 women, aged 42–52, and enrolled at seven sites throughout the United States. A subset of 949 women who had reached the menopause during the follow-up and who were not on HRT, were evaluated to investigate whether the incidence of metabolic syndrome increased during the menopause. The odds of developing metabolic syndrome per year were 1.45 (1.35–1.56) in perimenopausal women and 1.24 (1.18–1.30) after the menopause, $p = 0.001$. As secondary outcomes, all components of the metabolic syndrome, including BP, were assessed. SBP was found to slowly increase from 6 years before, peaking at 1.5 mmHg higher 1 year after the final menstrual period, but not significantly so ($p = 0.07$), leading the authors to report no effect of the menopause on BP [42].

The evidence for a putative protective role of sex steroids on BP as detailed earlier is compelling, but such effect is not conclusive from observational studies spanning the menopause. It thus deserves further examination through a careful scrutiny of the evidence provided from the clinical studies available to date, while future studies should be designed with BP as a primary end point.

## 27.5 Does Hormone Replacement Therapy Cause Hypertension in Normotensive Women? Case Control and Prospective Studies

Hypertension was the most common comorbidity reported in women on HRT in general [43], but whether this is simply an association or whether HRT is causal in increasing BP is controversial. Numerous studies have examined the effect of HRT on BP. In an extensive review from 1960 to 2004, Meuck described a somewhat
variable effect of oral HRT on BP in normotensive women, which may in part be explained by the various oral estrogen preparations used, and a more consistent beneficial effect when transdermal estradiol was used [44]. A more consistent BP-lowering effect of HRT became apparent when reviewing studies that used ABPM and in subjects receiving transdermal estrogen. In these studies, BP was lowered in 11 out of 13 studies using transdermal estrogen as opposed to only four out of 11 studies using oral estrogen formulations. In a more recent review, Ashraf and Vongpatanasian again underscored the beneficial effect of transdermal estrogen on BP; an effect, they proposed, which was likely due to the avoidance of the first-pass hepatic metabolism of estradiol [9]. In our update of the literature review since 2000, similar observations and conclusions were reached.

In a cross-sectional study of 35 normotensive postmenopausal women, Christ and colleagues showed that estrogen alone, either as oral 17β-estradiol or conjugated equine estrogen (CEE), over a 12-month period was associated with reduced ABPM systolic (−8 mmHg) and diastolic (−5 mmHg) daytime BP (p < 0.05), an effect that was offset when progestin, mainly in the form of oral medrogestone and norethisterone, was added [45]. In another cross-sectional study, Prelevic and colleagues studied 256 healthy postmenopausal women, divided into four groups according to the HRT used, i.e., tibolone, transdermal 17β-estradiol (with or without norethisterone acetate), oral CEE (with or without norgestrel), and control, and demonstrated a BP-neutral effect of all HRT combinations, in contrast to an increase in BP in the tibolone group, when compared to the controls [46]. Conclusions are limited, based on the varied estrogen and progestin compounds and combinations used.

Higashi and colleagues compared the impact of 0.625 mg CEE on forearm resistance artery endothelial function in three cohorts, including 10 hypertensive women, 35 normotensive women, 52 ± 4 years, BMI 22.6 ± 2.8 kg/m², compared to ten control subjects, 53 ± 4 years, BMI 23.1 ± 2.5 kg/m², over 12 weeks. The maximal forearm blood flow (FBF) response to reactive hyperemia increased over 12 weeks of CEE both in the hypertensive and normotensive groups whereas it remained unchanged in the control group. The augmentation of FBF response to reactive hyperemia evoked by the CEE was significantly greater in the hypertensive group than in the normotensive group (maximal FBF, 49 ± 8 vs. 17 ± 5 %, p < 0.05). The BP was measured before and after 12 weeks and did not reveal a difference between the two arms [47].

Sumino and colleagues examined the effect of 0.625 mg CEE with 2.5 mg MPA daily in 17 women, aged 53 ± 4 years, BMI 22.3 ± 2.4 kg/m², and 19 controls aged 52.6 ± 5.4 years, BMI 22.5 ± 2.4 kg/m², on clinic and ABPM. There were no differences in either clinic blood pressure, reported as the mean of three measurements after at least 10 min of rest, or on ABPM [48].

Lee and colleagues recently investigated the effect of 0.625 mg CEE daily on ABPM before and after 2 months of treatment in a noncontrolled study of 25 normotensive Korean postmenopausal women, mean age 56 ± 5.5 years, BMI 24 ± 1.64 kg/m², none of whom smoked or had diabetes. CEE increased both daytime SBP and DBP, an effect that tended to be abolished when micronized
progesterone was added [49]. Conversely HRT, in the form of oral and transdermal estrogen with progestin, diminished the rise in SBP over the years in healthy postmenopausal women compared to controls (7.6 vs. 18.7 mmHg, \( n = 77 \)) in a longitudinal observational study, a difference that intensified at older ages [50]. Similarly, the proportion of postmenopausal women who experienced a nocturnal drop in BP (dippers) reached 80% in HRT users, compared to 50% in non-HRT users, \( p = 0.048 \) [51]. Finally, in the Rancho Bernardo cross-sectional study of 1,044 postmenopausal women, all estrogen users, with more than 80% of participants on CEE, had a higher estimated glomerular filtration rate measured using the abbreviated modification of diet in renal disease equation and lower BP than non-users at study entry, after controlling for confounders. Similarly, at the 10-year follow-up, long-term current estrogen users showed an improvement in BP, with reduction in mean DBP among long-term current users, and an increase in mean SBP among those who never used HRT [21].

The neutral or beneficial effect of HRT on BP in postmenopausal women is in contrast to the clear elevations in BP that may occur when higher doses are given to younger women for oral contraception, especially with the oldest, first-generation birth control pills [52]. The difference in the results obtained in the studies mentioned may be explained by the different HRT preparations used (17\( \beta \)-estradiol vs. CEE, oral vs. transdermal, type of progestin used), the duration of HRT use, and the baseline characteristics of the study population.

27.5.1 Randomized Controlled Trials

The overwhelming evidence from large randomized controlled trials of HRT revealed a general neutral effect on BP, as detailed in Table 27.1. However, none of these studies were designed with BP as the primary outcome.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial [53] included 875 healthy normotensive postmenopausal women (mean age 56.1 years), who received various combinations of oral HRT with 0.625 mg CEE daily, either alone or in combination with various preparations of progestin (cyclic or continuous MPA, or cyclic micronized progesterone) for 3 years (see Table 27.1 for the details of the dose used). The study participants were mostly white with a mean age 56.1 ± 4.3 years, BMI 26 ± 4.5 kg/m\(^2\), and 68.7% had a natural menopause. SBP increased in all groups, whereas DBP remained uniform over time, though the BP effects did not differ significantly by treatment type. A distinctive characteristic of the PEPI cohort is the relatively high education level, 97% of women graduated from high school, 41% from college, and 29% had additional post-college education. Furthermore 49% were nonsmokers and two-thirds reported moderate physical activity.

In the Women’s Health Initiative (WHI) 16,608 postmenopausal women (mean age 63.3 years) were randomized to treatment with 0.625 mg of CEE and 2.5 mg of MPA daily versus placebo. An increase in SBP of 1 mmHg was noted in those
<table>
<thead>
<tr>
<th>Study/reference (year of publication)</th>
<th>Age range/year (mean ± SD)</th>
<th>Study duration</th>
<th>Number</th>
<th>Estrogen type/dose</th>
<th>Progestin type/dose</th>
<th>Δ SBP versus control or placebo mmHg (p value)</th>
<th>Δ DBP versus control or placebo mmHg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPI [53] (1995)</td>
<td>45–64 (56.1)</td>
<td>3 years</td>
<td>175</td>
<td>CEE(^b) 0.625 mg None</td>
<td>−1.7 (NS)</td>
<td>−1.5 (NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>174</td>
<td>CEE 0.625 mg       MPA(^c) 10 mg/d cyclical(^d)</td>
<td>−1.3 (NS)</td>
<td>−1.4 (NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>174</td>
<td>CEE 0.625 mg       MPA 2.5 mg/d</td>
<td>0.4 (NS)</td>
<td>−0.3 (NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>178</td>
<td>CEE 0.625 mg       Micronized progesterone 200 mg/d(^d) placebo</td>
<td>−2.5 (NS)</td>
<td>−2.2 (NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>174</td>
<td>Placebo            None</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>WHI [54] (2002)</td>
<td>50–79 (63.2 ± 7.1)</td>
<td>5.2 years</td>
<td>8506</td>
<td>CEE 0.625 mg       MPA 2.5 mg/d</td>
<td>1.5 (^e) (NA(^f))</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8102</td>
<td>Placebo            Placebo</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>WHI–CEE arm [56] (2004)</td>
<td>50–79 (63.3 ± 7.3)</td>
<td>6.8 years</td>
<td>5310</td>
<td>CEE 0.625 mg       None</td>
<td>1.1 (0.003)</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>(DOPS trial) [57] (2003)</td>
<td>45–58 (49.5 ± 2.7)</td>
<td>5 years</td>
<td>502(^g)</td>
<td>E(^h) 2 mg       Norethisterone 1 mg</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>EPAT [59] (2005)</td>
<td>46–81 (61 ± 7)</td>
<td>2 years</td>
<td>93(^i)</td>
<td>E(^h) 1 mg       None</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>88</td>
<td>Placebo            Placebo</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study/reference (year of publication)</th>
<th>Age range/year (mean ± SD)</th>
<th>Study duration</th>
<th>Number</th>
<th>Estrogen type/dose</th>
<th>Progestin type/dose</th>
<th>Δ SBP versus control or placebo mmHg(^a) (p value)</th>
<th>Δ DBP versus control or placebo mmHg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seely et al. [14] (2004)</td>
<td>50–72 (57.2 ± 5.6)</td>
<td>16 weeks(^i) cross over</td>
<td>21</td>
<td>CEE 0.625 mg</td>
<td>None</td>
<td>No change</td>
<td>−2 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td></td>
<td>Droloxfene 60 mg/ day</td>
<td></td>
<td>AmBP (No change)(^k)</td>
<td>AmBP (No change)(^k)</td>
</tr>
<tr>
<td>Sørensen et al. [60] (2000)</td>
<td>55 ± 6.3</td>
<td>24 weeks(^j)</td>
<td>16</td>
<td>E2(^h) 4 mg</td>
<td>Norethisterone acetate cyclic</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td>Placebo</td>
<td>Placebo</td>
<td>AmBP (No change)(^k)</td>
<td>AmBP (No change)(^k)</td>
</tr>
</tbody>
</table>

\(^a\) Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise  
\(^b\) CEE – conjugated equine estrogen  
\(^c\) MPA – medroxyprogesterone acetate  
\(^d\) Given for 12 days per month  
\(^e\) Systolic blood pressure was, on average, 1.0 mm Hg higher in women taking estrogen plus progestin at 1 year, rising to 1.5 mm Hg at 2 years and beyond  
\(^f\) NA-data not shown  
\(^g\) 6.6 % were hypertensive, women with intact uterus (n = 407) received norethisterone 1 mg for 12 days per cycle, 95 hysterectomized women didn’t receive any progestin  
\(^h\) E2-17- beta estradiol  
\(^i\) Healthy postmenopausal women with Low density lipoprotein cholesterol greater than 130 mg/dl  
\(^j\) Women received either CEE (0-625 mg/day) or droloxfene (60 mg/day) for 6 weeks and, after a 4-week washout, were restudied on the alternate medication, 12 days of MPA were administered at the end of the study to antagonize the effects of estrogen on the endometrium  
\(^k\) 24 hour ambulatory blood pressure was measured in 10 normotensive patients,  
\(^l\) cross over study in two 12-week periods separated by a 3-month washout
on HRT at 1 year, and of 1.5 mmHg at 2 years ($p$ value not available), with no change in DBP [54], an increase that was considered substantial given the large study population. Women in the WHI trial were not all normotensive, nevertheless they were considered to be representative of the US population: 84% were white, had a mean BMI 28 ± 5.9 kg/m², 40% were previous smokers, 10% were current smokers, 38% had hypertension, 64% were treated with antihypertensive medications, and BP was reported to be controlled in only 36% of subjects [55]. We are unaware of any subgroup analysis by baseline BP status. Similarly, in the CEE-only arm of the WHI, 10,739 postmenopausal women, with similar baseline characteristics as detailed previously, were randomized to treatment with 0.625 mg of CEE. At 1 year, SBP was higher by 1.1 (0.4) mmHg ($p = 0.003$) in women receiving CEE compared with the placebo group, and remained so throughout the follow-up, while no differences in DBP were noted between the two groups [56].

In the Danish Osteoporosis Prevention Study [57] (DOPS), 1,006 early menopausal women ($n = 502$, mean age 49.5 years), of whom 6.6% had hypertension at baseline, were randomized to HRT (2 mg oral estradiol combined with 1 mg norethisterone or not according to their hysterectomy status) or no HRT in an open label trial. HRT had no effect on either office SBP or DBP at any of the study time points (6 months, and 1, 2, and 5 years). HRT was terminated in three patients due to hypertension; in two of these, borderline hypertension was present before the initiation of HRT. High BP persisted after termination of HRT and normalized after the addition of antihypertensive therapy. In the third participant whose BP was normal before the initiation of HRT, BP normalized several years after termination of HRT.

The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) trial randomized 222 healthy postmenopausal women, mean age 61 years, with low-density lipoprotein (LDL) cholesterol >130 mg/dL (but no pre-existing cardiovascular disease) to 1 mg of unopposed oral 17β-estradiol or placebo for 2 years. Fifty-six percent of study subjects were white, with a mean BMI of 29 ± 6 kg/m², 45% nonsmokers, and 18% on antihypertensive drugs. The primary end point was the overall rate of progression of subclinical atherosclerosis, measured by carotid artery intima-media thickness (IMT), which was slower in patients taking unopposed estrogen compared with placebo [58]. Office BP was a prespecified end point. SBP and DBP declined in both study arms, but there were no differences between the HRT and placebo groups [59] in the subset of normotensive women. Treatment effects on SBP differed significantly by age of the subject; younger women had a rise in SBP on estradiol, while older women had a drop in SBP. These trials used different estrogen and progestin HRT regimens, while the DOPS and EPAT trials used 17β-beta estradiol, and the PEPI and WHI trials used CEE; and while DOPS used norethisterone, PEPI and WHI used MPA, and EPAT used no progestin.

Smaller studies using ABPM have demonstrated conflicting results on BP. In a double-blind crossover trial lasting 16 weeks, Seely and colleagues [14] evaluated the impact of 0.625 mg CEE daily versus droloxifene 60 mg daily on clinic BP
levels in 21 postmenopausal women, and on ABPM in a subset of 10 women. Study subjects were almost exclusively white, mean age 57.2 ± 5.6 years, with a mean BMI 27.3 ± 4.2 kg/m². There was no impact of either oral CEE or droloxifene on either clinic BP or ABPM.

Sorensen and colleagues [60] studied 16 postmenopausal women with a mean age of 55 ± 6.3 years, in a randomized crossover design study. Women received 4 mg of oral 17β-estradiol plus 1 mg of norethisterone or placebo. The participants were evaluated at four visits in each treatment period, at baseline and in the second, ninth and 11th week. Office BP demonstrated a decrease in SBP (-5.1 mmHg, \( p = 0.029 \)) and a decrease in DBP (-3.2 mmHg, \( p = 0.057 \)) in the second week, but BP returned to baseline after 9 weeks of combined HRT. As for the ABPM, when compared with placebo, changes from baseline in mean, minimum, and maximum BP (daytime, nighttime and mean 24-h values) were not significant after 9 weeks of combined HRT.

**27.6 Does Hormone Replacement Therapy Exacerbate Hypertension in Hypertensive Women? Case-Control and Prospective Studies**

Older observational studies investigating the effect of HRT in hypertensive women are scarce, and either found no change or a decrease in BP [44]. In our literature search since 2000, very few additional studies investigated this issue.

In the Rancho Bernardo study, investigators evaluated the impact of long-term exposure to HRT, mainly as 0.625 mg oral CEE, on BP and parameters of kidney function in 1,044 community-dwelling postmenopausal women, divided into current users, past users, and those who never used HRT [21]. The mean age of the study subjects was 71.9 ± 7.8 years, BMI 24.7 ± 4.2 kg/m², 54.7 % met the criteria for hypertension, 5.4 % for diabetes, 28.5 % were on antihypertensive medications, 68.5 % exercised three times a week, and 50.9 % were ever-smokers. Current HRT users were younger, less likely to have hypertension, more likely to have had a hysterectomy, and had lower BMI and lower serum creatinine. In the cross-sectional analysis, SBP in current HRT users was 134.9 ± 22.4 mmHg, past users 140.4 ± 22.9, those who never used HRT 140.2 ± 23.0, \( p = 0.001 \), the significance of which was lost when adjusted for age, weight, hypertension, smoking, and presence of hypertension or hyperlipidemia. DBP in current HRT users was 74.6 ± 9.3 mmHg, in past users 74.4 ± 9.4, in those who never used HRT 74.9 ± 9.7, \( p = 0.76 \); the difference, however, became significant on multivariate analyses. Current users were also reported to have lower odds of having chronic kidney disease, odds ratio (OR) = 0.66 (0.48–0.90) in the adjusted analyses.

At the 10-year follow-up, DBP was highest in those who never used HRT when compared with past and current users (difference = -2 mmHg, \( p = 0.04 \)), and over this follow-up period the DBP of those who never used HRT showed no significant age-adjusted change (\( p = 0.1 \)). Past users and current users showed
similar drops in age-adjusted DBP compared to baseline (−3.4 mmHg, \( p < 0.0001 \) and −4.4 mmHg, \( p < 0.0001 \), respectively). The SBP increased among those who never used HRT (mean increase 6 mmHg, \( p = 0.02 \)), but it did not differ in the past and current user groups. A firm conclusion for a protective effect of HRT and BP cannot be reached from this observational study because of the nature of the study design and the fact that it included relatively fit women, and thus the potential confounder of the healthy user effect.

Karalis and colleagues studied 161 early postmenopausal hypertensive women on different HRT preparations (39 % on CEE and MPA over 36 months. The mean age was 52.2 ± 6.6 years, 70 % were white, 44.1 % had surgical menopause, 76.9 % were overweight, and 21.7 % were smokers at study entry. Overall, there was no change in office SBP or DBP on HRT. However, seven subjects stopped HRT during the follow-up because of an excessive rise in BP noted on a single reading, and an increase in the average number of antihypertensive drugs taken was noted from 1.4 ± 1.1 to 1.7 ± 1.2, \( p < 0.05 \) [61].

Lee and colleagues [49] studied the impact of HRT on ABPM in 51 hypertensive women, aged 57.4 ± 5.1 years, BMI 25.8 ± 3 kg/m2, 50 % of whom were on antihypertensive medications, 8 % had diabetes, and were nonsmokers, who received HRT as CEE (with or without MPA) for 2 months. There was a significant decrease in daytime SBP from 143.6 ± 13.2 to 137.6 ± 13.1 mmHg, \( p < 0.005 \), and nonsignificant decrease in daytime DBP from 85.2 ± 9.6 to 83.4 ± 9.4 mmHg. The decrement in daytime SBP was more accentuated in the subset using micronized progesterone with CEE as opposed to CEE alone. Similarly, there was a significant decrease in nighttime SBP from 131.2 ± 17.4 to 126.6 ± 14.8 mmHg, \( p < 0.05 \), and a nonsignificant decrease in nighttime DBP from 76.5 ± 10.2 to 74.5 ± 9.5 mmHg after receiving HRT.

Sumino and colleagues [48] prospectively studied 61 Japanese early postmenopausal women, with mild-to-moderate hypertension, well controlled on antihypertensive medications for 3 years, for 1 year on 0.625 mg CEE and 2.5 mg MPA daily (\( N = 31 \)), and 30 control subjects who did not want to take HRT. The mean age of the study subjects was 53–54 years and their BMI was 25 kg/m2; they had clinic and ambulatory BP, as detailed earlier in the chapter in the subset of normotensive women. There was no significant decrease in office and 24-h ABPM in the HRT users.

Higashi and colleagues studied 18 hypertensive women, age 53 (± 4) years, 10 on HRT as 0.625 mg CEE and eight on no HRT therapy over 12 weeks. None of the study subjects were on any antihypertensive drugs, the entry SBP was 146–147 mmHg, and DBP was 90–91 mmHg. A nonsignificant decrease in SBP (Δ −1.4 mmHg) and DBP (Δ −2 mmHg) in the group receiving HRT versus control was reported [47].

Szcekas and colleagues [62] prospectively studied 34 postmenopausal women with treated hypertension (SBP 140–170 mmHg), mean age 53 years, on 2 mg 17β-estradiol and norgestrel (0.5 mg from day 12 to day 22) for 19 weeks, and demonstrated a significant drop in ABPM, with a mean SBP decreasing from 149.3 ± 6.1 mmHg to 140.3 ± 8.5 (\( p < 0.001 \)) and in mean DBP from
95.4 ± 4.7 to 92.4 ± 7.2 (p < 0.05). Interestingly the decrease in BP was lowest in the subset of 11 women on calcium channel blockers.

In summary, the studies reviewed in this section show a neutral or slightly beneficial effect of oral HRT on BP in hypertensive women that is more likely to be detected in studies that used ABPM monitoring. A major limitation of these observational studies includes their small sample size, the variation in HRT regimens and combinations used, and a lack of control subjects. Hence, there is the need for randomized controlled trials to investigate the effect of HRT on this high-risk population.

### 27.6.1 Randomized Controlled Trials

There are no large clinical trials that studied the effect of HRT on BP in a population limited to hypertensive postmenopausal women. However, several of the large trials included a sizeable percentage of hypertensive women. Many of these studies, however, did not analyze the hypertensive women as a separate subset. These are detailed in Table 27.2 and are discussed in this section.

The Heart and Estrogen–Progestin Replacement Study (HERS) was a randomized placebo-controlled trial of 2,763 postmenopausal women with coronary heart disease (CHD), mean age 66.7 (±6.7) years, followed up for 4.2 years to determine the effect of HRT (CEE and MPA) in the secondary prevention of CHD [63]. Thirty-nine percent of the patients were hypertensive, 13 % current smokers, 23 % diabetic, 48 % of normal BMI, and 39 % exercised regularly. Clinic BP was determined and pulse pressure was calculated, but changes in BP were not the primary outcomes of the study. Mean SBP and DBP were 135 (±19) mmHg and 73 (±10) mmHg at study entry, and over 4.2 years there was an increase in SBP of 1 mmHg (p = 0.0001) with no change in DBP in women receiving HRT. There was a significant 2 mmHg increase in mean pulse pressure as compared to women in the placebo group (64 ± 17 mmHg vs. 62 ± 17 mmHg, p = 0.04) [64]. Changes in BP with HRT were not presented for the two subgroups of normotensive versus hypertensive women.

The Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) trial was designed to determine whether HRT can slow the progression of atherosclerosis, measured as carotid intima-media thickness (IMT) in 321 women, mean age 58.3 (±4.5) years. Study subjects were randomized to either oral 1 mg 17β-estradiol with standard-dose cyclic gestodene (0.025 mg gestodene on days 17–28 of each 4-week cycle), or oral 1 mg 17β-estradiol with low-dose gestodene (0.025 mg addition in each third cycle only), or no treatment. More than 50 % of subjects were hypertensive, on no antihypertensive medications, and had increased IMT in >1 segment of the carotid arteries at study entry. Office DBP decreased in the HRT groups as compared to the controls, by −4 mmHg in the standard gestodene group, p = 0.027, and −4.7 mmHg in the low-dose gestodene group, p = 0.008. During the follow-up, 29 subjects were started on antihypertensive
<table>
<thead>
<tr>
<th>Study/reference</th>
<th>Age range (year)</th>
<th>Study duration</th>
<th>Number</th>
<th>Estrogen type/dose</th>
<th>Progestins Type/dose</th>
<th>Δ SBP versus placebo or control mmHg\textsuperscript{a} (p value)</th>
<th>Δ DBP versus placebo or control mmHg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERS [64] (1998)</td>
<td>44–79 (66.7 ± 6.7)</td>
<td>4.1 years</td>
<td>1380\textsuperscript{b}</td>
<td>CEE 0.625 mg</td>
<td>MPA 2.5 mg/day</td>
<td>1 (&lt;0.0001)</td>
<td>No change</td>
</tr>
<tr>
<td>Placebo</td>
<td>1383</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHOREA [65] (2001)</td>
<td>40–70 (58.3 ± 4.5)</td>
<td>48 weeks</td>
<td>76\textsuperscript{c} 60</td>
<td>E\textsuperscript{2} 1 mg</td>
<td>Standard gestodene dose\textsuperscript{e}</td>
<td>3 (NS)</td>
<td>−4 (0.027)</td>
</tr>
<tr>
<td>E\textsuperscript{2} 1 mg</td>
<td>Low dose gestodene\textsuperscript{f}</td>
<td>Control</td>
<td>−1.2 (NS)</td>
<td>−4.7 (0.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaya et al. [31] (2006)</td>
<td>51.2 ± 0.4</td>
<td>1 year</td>
<td>31\textsuperscript{g}</td>
<td>E2 1 mg</td>
<td>Dydrogesterone 10 mg/day\textsuperscript{h}</td>
<td>AmBP daytime</td>
<td>AmBP daytime −1.7 (p &lt; 0.01)</td>
</tr>
<tr>
<td>32</td>
<td>Control</td>
<td>Control</td>
<td>AmBP nighttime −1.6 (p &lt; 0.01)</td>
<td>AmBP nighttime NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumino et al. [66] (2006)</td>
<td>48–66 (54.8 ± 3.6)</td>
<td>1 year</td>
<td>28</td>
<td>CEE 0.625 mg</td>
<td>MPA 2.5 mg/day cyclical\textsuperscript{i}</td>
<td>−3.1 (NS)</td>
<td>0.3 (NS)</td>
</tr>
<tr>
<td>27</td>
<td>Control</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPAT* [59] (2005)</td>
<td>46–81 (61 ± 7)</td>
<td>2 years</td>
<td>18\textsuperscript{l}</td>
<td>E2 1 mg</td>
<td>None</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>23</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manhem et al. [68] (2010)</td>
<td>51–65 (56)</td>
<td>1 year\textsuperscript{k}</td>
<td>20</td>
<td>CEE 0.625 mg</td>
<td>MPA 0.5 mg/day</td>
<td>−4 (NS); AmBP 2 (NS)</td>
<td>−2 (NS); AmBP 1 (NS)</td>
</tr>
<tr>
<td>Cross over</td>
<td>20</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study/reference</th>
<th>Age range (year)</th>
<th>Study duration</th>
<th>Number</th>
<th>Estrogen type/dose</th>
<th>Progestins Type/dose</th>
<th>Δ SBP versus placebo or control mmHg*</th>
<th>Δ DBP versus placebo or control mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvey et al. [67]</td>
<td>48–60</td>
<td>16 weeks¹</td>
<td>14</td>
<td>CEE 0.3 mg</td>
<td>MPA 10 mg/day cyclicalm</td>
<td>−7 (&lt;0.05); AmBP 1 (NS)</td>
<td>−2 (NS); AmBP 1 (NS)</td>
</tr>
<tr>
<td></td>
<td>(2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>CEE 0.625 mg</td>
<td>MPA 10 mg/day cyclicalm</td>
<td>−7 (&lt;0.05); AmBP -1 (NS)</td>
<td>−3 (NS); AmBP-1 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CEE 1.25 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(55)</td>
<td>Cross over</td>
<td></td>
<td></td>
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</tbody>
</table>

* Difference in systolic and diastolic measured in clinic unless otherwise specified

¹ Coronary heart disease patients, with 39% being hypertensive
² Patients had increased intima-media thickness (IMT) in ≥1 segment in carotid arteries; blood pressure ranged from optimal to stage 2
³ E2 = 17β-estradiol
⁴ Standard dose gestodene—addition of 0.025 mg gestodene on days 17–28 of each 4-week cycle
⁵ Low-dose gestodene (addition in each third cycle only)
⁶ Newly diagnosed mild-to-moderate hypertension
⁷ Dydrogesterone 10 mg per day for 14 days of each 28-day cycle
⁸ MPA 2.5 mg/day for 12 days a month
⁹ Hypertensive postmenopausal women with low-density lipoprotein cholesterol >130 mg/dL
¹⁰ Crossover design: each subject received 6 months of HRT and 6 months of placebo
¹¹ Randomized double-blind four-phase crossover design. Each phase lasted 4 weeks. MPA 10 mg/day was added for the final 14 days of each 28-day cycle
¹² MPA was given for the final 14 days of each 28-day cycle

ABPM ambulatory blood pressure monitoring, CEE conjugated equine estrogen, E2 estradiol, EPAT estrogen in the prevention of atherosclerosis trial, HERS heart and estrogen–progestin replacement study, MPA medroxyprogesterone acetate, PHOREA postmenopausal hormone replacement against atherosclerosis (trial)
medication: four subjects in the standard gestodene group, 12 in the low-dose gestodene group, and 13 in the control group ($p = \text{NS}$ intervention groups vs. control) and these subjects were excluded from analysis [65].

In the hypertensive subset group of the EPAT trial [59], detailed previously, 18 hypertensive women, mean age $61 \pm 7$ years, received 1 mg $17\beta$-estradiol and 23 women received placebo. No differences could be detected, either in office SBP or DBP, between the two groups.

Kaya and colleagues [31] studied 63 postmenopausal women, mean age $51.2 \pm 0.4$ years, with mild or moderate hypertension randomly assigned to receive either HRT with 1 mg/day micronized $17\beta$-estradiol sequentially combined with 10 mg/day dydrogesterone ($n = 31$, BMI $37.4 \pm 0.4$ kg/m$^2$) for 14 days of each 28-day cycle, or no therapy ($n = 32$, BMI $38.1 \pm 0.8$ kg/m$^2$) over a 12-month period. Mean ABPM dropped significantly in the HRT group ($-2.2$ mmHg, $p < 0.01$); in addition, ambulatory daytime SBP remained unchanged whereas nighttime SBP decreased significantly by $-1.6$ mmHg ($p < 0.01$). Conversely, ambulatory daytime DBP decreased significantly by $-1.7$ mmHg ($p < 0.01$) in the HRT group whereas nighttime DBP remained unchanged.

Sumino and colleagues [66] randomly assigned women to one of three groups for a 12-month study: a continuous oral CEE (0.625 mg/day) plus a cyclic oral MPA (2.5 mg/day, for 12 days per month), $n = 28$, mean age $54.8 \pm 3.6$ years, BMI $22.7 \pm 1.8$ kg/m$^2$; continuous transdermal $17\beta$-estradiol (absorption rate, 36 $\mu$g/day) plus cyclic oral MPA (2.5 mg/day, for 12 days per month), $n = 28$; mean age $55.2 \pm 5.1$ years; BMI $22.4 \pm 3.3$ kg/m$^2$; and a control group who did not receive HRT, $n = 27$; mean age, $55.9 \pm 5.7$ years, BMI $23.4 \pm 2.0$ kg/m$^2$. Eight untreated hypertensive subjects in the CEE + MPA group, seven subjects in the transdermal estradiol group, and seven subjects in the control group were included; information on whether the other participants were normotensive or controlled by antihypertensive medications was not available. There was no impact of the oral or the transdermal estrogen on BP.

Harvey and colleagues [67] studied 14 postmenopausal women, mean age 55 years, in a crossover 16-week study, where they used different preparations of CEE (0.3, 0.625, and 1.25 mg) combined with 10 mg/day MPA. Office SBP decreased significantly in the groups receiving CEE at the 0.3 and 0.625 mg doses, whereas office DBP decreased significantly only in the group receiving CEE at the 0.625 mg dose compared to placebo. ABPM remained unchanged.

In the randomized, double-blind, crossover study carried out by Manhem and colleagues [20], 20 well-controlled hypertensive postmenopausal women, mean age 56 years, BMI $27.6$ kg/m$^2$, received 6 months of HRT (CEE 0.625 mg daily plus MPA 0.5 mg daily) and 6 months of placebo, on top of their antihypertensive treatment. None of the participants were smokers or diabetic and half of them were on RAAS-blocking agents. Office- and ambulatory-measured SBP and DBP did not change significantly.

There was no change or a decrease in BP with different preparations of HRT except for the HERS trial; this might be explained by the high-risk population and/or the large sample size of the study population.
27.7 Transdermal Estrogen and Blood Pressure

27.7.1 Case-Control and Prospective Studies

Transdermal estrogen enters the circulation directly, bypassing the first pass through the liver, and unlike oral estrogen, does not result in an unfavorable cardiovascular profile, i.e., an elevation in serum C-reactive protein and triglyceride levels, a decrease in LDL particle size, and an increase in the production of certain coagulation factors [68]. In addition, transdermal estradiol is not associated with an increase in angiotensinogen levels [69].

In a large-scale clinical surveillance study, the effect of transdermal estradiol on BP in 13,910 postmenopausal women, of whom 1,516 had hypertension, was evaluated over a 2-month observation period. The authors reported no effect of transdermal estradiol in the normotensive participants, whereas they noted a decrease in SBP and DBP in hypertensive women. In the subgroup of 1,397 women with DBP $\geq 100$ mmHg before HRT initiation, there was a mean decrease of 7 mmHg in SBP and 9 mmHg in DBP, but specific details regarding HRT preparations in terms of doses and $p$ values for significance were not provided [70].

Zacharieva and colleagues studied 16 normotensive postmenopausal women, mean age $49.1 \pm 3.5$ years, BMI $24.1 \pm 2.4$ kg/m$^2$, who received transdermal estradiol 50 $\mu$g for 3 months. The participants were compared to 25 healthy young women with a mean age of $28.4 \pm 1.4$ years, BMI $23.87 \pm 1.4$ kg/m$^2$. No change was detected in office BP compared to baseline, whereas daytime, nighttime, and mean 24-h ambulatory SBP all decreased significantly by $-6.75$, $-5.8$, and $-5.5$ mmHg, respectively, $p < 0.05$ [71].

Kawecka-Jaszcz and colleagues studied 76 women with natural menopause, with mild-to-moderate hypertension for $5.9 \pm 5$ years, over 1 year: 40 women with a mean age of $52.5 \pm 5.8$ years, BMI $28.3 \pm 4.8$ kg/m$^2$, who took transdermal $17\beta$-estradiol and oral norethisterone acetate, and 36 control subjects, with a mean age $53.6 \pm 5.9$ years, BMI $27.0 \pm 3.6$ kg/m$^2$. BP at 1 year did not differ significantly from baseline values in either group [72].

Randomized trials describing the effect of transdermal HRT in normotensive and hypertensive subjects, published since 2000, are described in Tables 27.3 and 27.4 and discussed in the following section.

27.7.2 Randomized Controlled Trials in Normotensive Women

Seely and colleagues studied the effect of transdermal estradiol (two 0.1 mg patches twice a week) with (intravaginal micronized progesterone 300 mg/day) and without progesterone on 24-h ABPM in a randomized, placebo-controlled, crossover study of 15 healthy postmenopausal women, mean age $56 \pm 1.5$ years, BMI $24.9 \pm 0.9$ kg/m$^2$. Nocturnal SBP ($110 \pm 3$ mmHg), DBP ($63 \pm 2$ mmHg), and mean BP ($77 \pm 2$ mmHg) dropped significantly ($p < 0.02$) in the transdermal estradiol group compared with placebo. The mean decrease in SBP was $-6$ mmHg,
<table>
<thead>
<tr>
<th>Study/reference</th>
<th>Age range (year)</th>
<th>Study duration</th>
<th>Number</th>
<th>Dose of transdermal estradiol</th>
<th>Progestins type/dose</th>
<th>Δ SBP versus placebo or control mmHg (p value)</th>
<th>Δ DBP versus placebo or control mmHg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seely et al. [74] (1999)</td>
<td>56 ± 1.5</td>
<td>8 weeks</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>200 µg/day</td>
<td>None</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intravaginal Micronized Progesterone</td>
<td>AmBP-6 (night) (&lt;0.02)</td>
<td>AmBP-5 (night) (&lt;0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>200 µg/day</td>
<td>Placebo</td>
<td>No change</td>
<td>AmBP-7 (night) (&lt;0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>AmBP-8 (night) (&lt;0.02)</td>
<td></td>
</tr>
<tr>
<td>Vongpatanasin et al. [75] (2001)</td>
<td>53 ± 2</td>
<td>8 weeks</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>200 µg/day</td>
<td>None</td>
<td>AmBP no change</td>
<td>AmBP-2 (0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ichikawa et al. [76] (2008)</td>
<td>57 ± 8.1</td>
<td>24 months</td>
<td>22</td>
<td>36 µg/day</td>
<td>MPA 2.5 mg/day&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−9 (NS)</td>
<td>−7.1 (&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise
<sup>b</sup> Cross over design
<sup>c</sup> No difference in daytime systolic or diastolic blood pressure was found
<sup>d</sup> MPA-Medroxyprogesterone 2.5 mg/day for 12 days per month

ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, MPA Medroxyprogesterone, SBP systolic blood pressure
<table>
<thead>
<tr>
<th>Study/reference (year of publication)</th>
<th>Age range (year)</th>
<th>Study duration</th>
<th>Number</th>
<th>Dose of transdermal estradiol</th>
<th>Progestins type/dose</th>
<th>Δ SBP versus placebo or control mmHg&lt;sup&gt;a&lt;/sup&gt; (p value)</th>
<th>Δ DBP versus placebo or control mmHg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinito et al. [76] (2001)</td>
<td>53.5 ± 4.5</td>
<td>6 months</td>
<td>30</td>
<td>50 µg/day</td>
<td>MPA 10 mg/day cyclical&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No change; AmBP-5.5 (&lt;0.05)</td>
<td>No change; AmBP-6.5 (&lt;0.05)</td>
</tr>
<tr>
<td>Sumino et al. [66] (2006)</td>
<td>48–66</td>
<td>1 year</td>
<td>28</td>
<td>36 µg/day</td>
<td>MPA 2.5 mg/day cyclical&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−6.6 (NS)</td>
<td>−3.6 (NS)</td>
</tr>
<tr>
<td></td>
<td>54.8 ± 3.6</td>
<td></td>
<td>27</td>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Difference in systolic and diastolic blood pressure measured in clinic unless specified otherwise

<sup>b</sup> 10 mg/day from day 17 to 28

<sup>c</sup> 2.5 mg/day for 12 days a month

ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, MPA medroxyprogesterone acetate, SBP systolic blood pressure
in DBP it was $-5$ mmHg, and in mean BP it was $-5$ mmHg. The addition of progesterone resulted in no further drop in BP [73].

Vongpatanasin and colleagues [74] studied 12 postmenopausal women, mean age $53 \pm 2$ years, BMI $28.5 \pm 1$ kg/m$^2$ over 8 weeks. All subjects received each of the following three regimens in random order according to a single-blind crossover design: transdermal estradiol alone as two 0.1 mg patches twice a week (200 μg/day) for 8 weeks, oral CEE 0.625 mg for 8 weeks, and a placebo patch (two patches twice a week) plus oral placebo for 8 weeks. There was no change in BP on the oral CEE, whereas transdermal estradiol resulted in a significant decrease in 24-h BP by $-2$ mmHg ($p < 0.01$) compared to placebo, but no change was observed in SBP.

Ichikawa and colleagues studied 22 postmenopausal women, mean age $57.1 \pm 8.1$ years, BMI $22 \pm 3$ kg/m$^2$, randomized to transdermal HRT as continuous 17β-estradiol patch at 36 μg/day plus cyclic oral MPA 2.5 mg/day for 12 days/month for 24 months. DBP and mean BP were significantly decreased at 12 and 24 months. DBP decreased from $74.6 \pm 9.4$ to $67.5 \pm 5.9$ at 24 months; similarly, mean BP decreased from $90.1 \pm 9.6$ to $82.2 \pm 7.0$ ($p < 0.05$ for both), whereas SBP only tended to decrease [75].

### 27.7.3 Randomized Controlled Trials in Hypertensive Patients

Affinito and colleagues [76] randomized 60 postmenopausal women with treated mild-to-moderate hypertension, mean age $53.5 \pm 4.5$ years, BMI $25 \pm 3$ kg/m$^2$, to transdermal estradiol at a dose of 50 μg/day combined with MPA 10 mg/day or placebo over 6 months. Office and 24-h ABPM were measured. No change in office BP was observed, whereas mean 24-h ambulatory SBP and DBP decreased significantly in the treatment group, by $-5.5$ mmHg and $-6.5$ mmHg respectively, compared to placebo. The diurnal changes were analyzed separately and both SBP and DBP decreased significantly for the daytime, but not nighttime, measurements.

Sumino and colleagues [66] found in their study detailed earlier in the chapter a nonsignificant decrease in clinic SBP and DBP in 28 postmenopausal women, mean age $54.8 \pm 3.6$ years who received transdermal estradiol (36 μg/day) with MPA 2.5 mg/day for 12 months [66].

Ashraf and colleagues [9] reviewed the impact of transdermal estradiol in hypertensive women in eight prospective randomized trials and reported a trend for a decrease in SBP and DBP on 24-h ABPM measurements, with a weighted mean average change of $-4.9$ mmHg for SBP and $-2.3$ mmHg for DBP [9].

In general, randomized trials of transdermal estrogen in hypertensive women are small and reveal either no change or a significant decrease in BP, with the latter most likely to be detected in studies that included ABPM monitoring. The pattern for the decrease in SBP, DBP, daytime, and nighttime, was not very consistent across studies, probably reflecting their suboptimal monitoring of BP changes and/
or low power. Of interest, studies comparing oral versus transdermal estrogen yielded somewhat different results, some of them showed a reduction in BP in the transdermal group versus the oral group [77, 78], while others found a similar decrease in BP in both groups [79]. Thus, larger trials with longer duration and more careful serial BP assessment on follow-up are needed.

### 27.8 Conclusions

Hypertension is a major risk factor for cardiovascular diseases in both genders and accounted for 12.8% of all deaths worldwide in 2008. The proportion of subjects with hypertension clearly increases with age in both genders, being higher in men before the age of 45 years, and then in women after the age of 65 years. Observational studies that examined changes in BP across the menopause have, however, led to mixed results. Physiological studies evaluating the impact of HRT on regulators such as the RAAS, sympathetic system, and markers of endothelial function and inflammation, have not led to consistent results. Observational studies that examined changes in BP across the menopause, and which investigated the impact of HRT on BP in hypertensive and normotensive women, have also provided mixed results. The above illustrates the complexity of the homeostatic systems involved and the heterogeneity of the studies in terms of the HRT regimens used, subjects characteristics, and study duration. The ultimate evidence emerging from randomized controlled trials of HRT reveal an overall BP-neutral effect of the oral preparations and a BP-lowering effect of transdermal estrogen, and possibly micronized progesterone, dydrogesterone, and drosperinone, both in normotensive and hypertensive women. The BP-lowering effect of transdermal HRT is best illustrated in studies that assessed 24-h ABPM.

Although the use of HRT has declined substantially over the last decade due to cardiovascular concerns and cancer adverse events, as revealed in the HERS, PEPI, and WHI trials, HRT protects from menopause-associated bone loss, can be beneficial for several other menopause-associated morbidities (mood, sleep, memory, some quality of life measures), and remains the most effective treatment for the vasomotor symptoms associated with the menopause.

Scrutiny of the data presented in this review with regards to the impact of HRT on BP suggests an overall BP-neutral effect of oral HRT and a neutral and/or lowering BP effect of transdermal estrogen. As HRT provides relief from vasomotor symptoms, HRT may decrease BP in the subset of women with these symptoms, although this hypothesis remains to be tested. The International Menopause Society, with the participation of the Task Force on Gender of the European Society of Cardiology, in its consensus workshop stated that HRT is not contraindicated in women with hypertension and, in some cases, it may even reduce BP. However, it recommended that BP be carefully monitored and well-controlled in women on HRT [80]. In its 2010 position statement, the North American Menopause Society stated: “The benefit–risk ratio for menopausal HRT is favorable for women who initiate HRT.
close to menopause [81]”. Studies are, however, relatively scarce and have the major limitations detailed earlier, and thus there is a clear need for trials to be conducted in a younger population using different HRT preparations.

The ongoing Early versus Late Intervention Trial with Estradiol (ELITE) trial and the Kronos Early Estrogen Prevention Study (KEEPS) may provide some insight on the characteristics of individuals who are most likely to benefit from HRT [82, 83]. ELITE is a 4-year trial recruiting 643 postmenopausal women to be randomized to 1 mg of 17β-estradiol versus placebo (with 4% vaginal progesterone in women with an intact uterus) in women within 6 years of the menopause versus >10 years post-menopause, with the primary end point being the rate of change of the distal carotid IMT and the secondary end points of neurocognitive function, coronary artery lesion, and calcium score by cardiac computed tomography. KEEPS is a 4-year trial recruiting 720 early postmenopausal women randomized to oral CEE 0.45 mg or 5 μg of transdermal estradiol, along with 200 μg micronized progesterone administered cyclically, with the primary end point of carotid IMT, and multiple secondary end points, including change in coronary calcium score by X-ray tomography, plasma lipid profiles, blood clotting factors, inflammatory markers, hormone levels, cognitive and affective scores on standard psychometric tests, and quality of life. None of the studies prespecified BP as an outcome, but it is hoped that it will be captured as part of a visit exams in both studies. If so, both studies may shed light on whether the HRT effects on BP differ according to time since the menopause.

The majority of women, be they hypertensive or normotensive, do not experience any change in BP on oral HRT, and on average show a consistent decrease on the transdermal preparations. Transdermal estrogen in combination with micronized progesterone, dydrogesterone, or drospirenone may be a preferred option for normotensive women, and even hypertensive women, with menopausal symptoms, with careful BP monitoring. Most individuals are anticipated to do well, though exceptions do exist. Therefore, the challenge is to identify individuals at risk for developing hypertension on HRT, and avoid its use in such cases, if possible. Risk profiling, at present, is through a careful clinical assessment of the patient’s characteristics, including vasomotor symptoms, age, family history, and lifestyle. In the future, it is anticipated to be complemented by genotype profiling, to identify genes or polymorphisms that increase the risk, for some individuals, to develop hypertension in general and hypertension on HRT in particular, e.g., estrogen receptors and renin polymorphisms.

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