



Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women

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Abstract

High blood pressure (BP) ranks as the greatest risk factor for cardiovascular disease. The increased cardiovascular risk determined in recent interventional studies has led the health authorities in some countries to re-ignite the discussion about whether hypertension should be listed as a contraindication for hormone replacement therapy (HRT). We reviewed papers published since 1960 and listed in MEDLINE, EMBASE and Biosis, on studies that monitored the course of BP during HRT.

We found that both primarily normotensive and hypertensive postmenopausal women actually run only a very low risk of BP increase during HRT, indeed, BP was often lowered. In one of our own studies 1397 hypertensive women with BP diastolic >95 mmHg received transdermal HRT regimens; BP was lowered by an average of 7 mmHg systolic and 9 mmHg diastolic. The results of the more recent 24-h ambulatory BP studies are particularly conclusive. At least 19 such studies have been performed, 13 placebo-controlled and 10 cross-over; 5 found no effect on BP and 14 studies demonstrated BP reductions. BP was lowered by treatment with transdermal estradiol in 11 of 13 studies and by oral estrogen in 4 of 11 studies. The effects were not consistent with regard to systolic or diastolic BP nor to action on day- and night-time BP.

It cannot be ruled out that some women with a particular predisposition exhibit an abnormal reaction to the vasoactive effects of HRT, and there is a paucity of long-term data on risk populations, specifically on the progestogenic effects in patients with pre-existing arteriosclerotic lesions. In conclusion, the risk of developing hypertension during HRT is very low, but hormone therapy should always be appropriately indicated and during therapy BP should be checked regularly.

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1. Introduction

The issue of a possible association between hormone (replacement) therapy (HRT) and hypertension originates from studies on oral contraceptives (OC).

Long-term OC use is known to raise systolic blood pressure (BP) relatively frequently, and diastolic values less frequently, with 2–5% of patients exhibiting a rise in BP by 6–8 mmHg and also to serious hypertension [1–3]. The risk is clinically relevant. Notably, one large WHO study found hypertensive OC users to have a higher risk of heart attack and stroke [4]. The causality between the development of hypertension and OC has been proven since high BP is usually

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reversible after OC are discontinued. About 25% of women remained hypertensive for up to over a year after stopping OC. Presumably, most of these women had been suffering from latent hypertension which became manifest as a result of the oral contraceptive's action [1,3,5].

To date, reports of BP elevations on HRT have only been the exception. Despite this low prevalence, pre-existing hypertension has been listed as a relative or absolute contraindication in the prescribing information of most hormone replacement drugs for many years now. This started long before the one study arm of the Women's Health Initiative (WHI) [6] was prematurely terminated in May 2002, triggering, as we all know, wide-spread discussions and demands for a re-evaluation of HRT (e.g. [7,8]). As far as Germany is concerned, the Federal Institute for Drugs and Medical Devices (BfArM) in February 2003 launched a regulatory investigation into all hormone replacement drugs specifically aimed at exploring their cardiovascular risks. Now that such a large number of women with hypertension have been studied by the WHI (36%), the German Health Authorities are currently seriously considering listing hypertension as a contraindication for HRT. The reason is the elevated cardiovascular risks established by the WHI study, and the high proportion of hypertensive women in this trial.

This situation has inspired us to carry out an up-to-date systematic review of the studies published since 1960. Included were studies which measured BP changes in normotensive and hypertensive patients receiving HRT. Included also is a brief evaluation of the mechanisms of action according to which BP changes on HRT might be expected. The main results from the large number of studies will be presented in the following review and particularly include detailed lists of the most conclusive studies that utilized ambulatory 24-h BP monitoring.

2. Methods

Regarding our *search strategy* the literature review included a search in MEDLINE since the start of this database in January 1969 (reviewing studies on HRT since 1960) which was the prime source for this report. In addition we searched in the databases EMBASE and Biosis for studies since 1990. The

search was primarily limited to English-language articles. To be considered for inclusion, publications had to be original articles. Key words were 'estrogen replacement therapy,' 'hormone replacement therapy,' 'estrogen/progestogen therapy,' 'blood pressure,' 'hypertension,' 'hypertensive patients' and 'normotension.' Searches included also combination of these terms with the key words 'menopause,' 'postmenopause' or 'natural menopause' and 'surgical menopause.' Both authors selected and extracted the studies followed by double-checking both literature searches and data extraction.

We used free text searching as well as MeSH headings and to retrieve trials for the following selection (*Quorum diagram, i.e. flow diagram on selection of papers*):

- (1) Observational studies: case/control and cohort studies, evaluating normotensive and/or hypertensive patients, respectively, frequently evaluated in the same studies.
- (2) Prospective randomized studies without 24 h BP measurements, (a) in normotensive and (b) in hypertensive patients. A randomized controlled trial had to include a placebo or control group with evidence of random allocation to study intervention and represent either a parallel or a cross over design.
- (3) All studies (independent of study design) with 24 h-ambulatory blood pressure measurements in (a) normotensive and (b) hypertensive patients.

Studies of groups (1) and (2) were described only in summary. Single examples were used to point on practically relevant results. However, all studies found with 24-h ambulatory blood pressure measurements were recorded and listed in tables. Thereby we also used hand search of the relevant journals published since 1995. In the assessment of these studies the placebo-controlled cross-over trials had the highest priority followed by placebo-controlled trials with parallel study design, and followed by studies using an open study design versus a control group.

This procedure is according to the 'Jadad criteria' for systematic reviews [9]. The most important items are randomization and blinding. However, it has to be stressed that the diagnostic method in assessing the effects of HRT on BP has the highest priority. Twenty-four hours BP evaluation has been proven as

the method of choice to assess changes of blood pressure during any drug therapy and therefore we assessed these studies primarily independent from the study design.

Of course the problem can occur that smaller studies may bias the conclusion. It appears that especially the studies with the highest priority, i.e. studies with 24 h ambulatory BP measurements, were performed with comparable patient numbers, particularly the important comparison of studies with normotensive or hypertensive women, respectively. Furthermore, regarding this point, a comparable number of studies is available using a cross-over design and placebo group, being a good requirement for a comprehensive assessment of similar studies so that special smaller studies may not bias the conclusion.

The essential parameters, which were recorded during the literature search, were significant BP changes (24 h BP evaluation during day and night) with informations on choice of HRT, differentiated in terms of estrogen only (ET) and estrogen/progestogen (EPT) therapies (sequentially sEPT and continuously cEPT). Furthermore duration of ET or EPT as well as informations on patient number for hormone and control group were registered. Inability to evaluate those parameters in the publications led to exclusion of the papers from this review. Of course apparent double publications also were excluded.

The present review is of qualitative and empirical nature, no statistical analysis was used to compare the various studies. The prime objective was to evaluate which kind of studies with careful BP measurements during HRT are available up to now and if there are data justifying a general specification of 'hypertonus' as a contraindication. Furthermore the plausibility shall be evaluated in as far there could be an increased risk under consideration of possible mechanisms which may have an influence on BP.

2.1. Estrogens' mechanisms of action

Vasodilation is the most important effect estrogen has on the arterial vessel. Vasodilation can be caused by a number of different mechanisms primarily involving a direct effect on smooth muscle driven by vasodilative mediators, and actions on the ion channels [10]. Most recent evidence derived from own and other studies suggests that estrogen metabolites also

show vascular activity, sometimes at very low concentrations and stronger than the substrate estradiol (reviewed in Ref. [11]). Estrogen's vasodilative effects should result in a primary reduction in BP. This action has been described in experimental models (e.g. [12–15]) as well as in a number of clinical studies reported in this review.

However, healthy bodies, it should be noted, will usually rapidly and most effectively antagonize effects which might cause changes in BP. One example of a possible estrogenic effect that might elevate BP is the interaction with the renin–angiotensin–aldosterone system (RAAS). However, even the effects on this system should lead to non-reversible BP increases in exceptional cases only. Oral estrogens can elevate the production of the renin substrate formed in the liver. For instance, 1.25 mg of conjugated equine estrogen can cause an elevation of 250%, which is comparable with the effect of 20 µg ethinyl estradiol [16]. However, this does not lead to hypertension per se since the overproduction of aldosterone stimulated by angiotensin II hampers the production of renin in the kidneys. By means of negative feedback within the RAAS control system, the system is kept in a state of equilibrium. Therefore, the studies observed relative normal plasma renin activities despite the increased production of renin substrate and aldosterone. However, this primarily applies to functioning control systems, i.e. to healthy women. A disposition-related dysregulation of the RAAS is presumably needed before the stimulation of renin substrate ultimately leads to a net increase in the vasoconstrictive angiotensin II or to increased sodium and water retention, and consequently to hypertension.

Thus, it can be expected that estrogens, despite their many vasoactive mechanisms, cause changes in BP in exceptional cases only, namely when the individual has a predilection or a pre-existing cardiovascular disease. With regard to the example mentioned of the effect of estrogens on the RAAS it is discussed that equine estrogens, because they are mostly formulated with heterologous estrogens [17], can, in approx. 5% of the women, also cause abnormal hepatic proteins to form such as abnormal renin substrate, resulting in unphysiological angiotensin I/II cleavage products. These might escape the physiological feedback control, causing idiosyncratic and/or iatrogenic hypertension [18–21]. That is one reason why a switch to

estradiol preparations is recommended when a woman develops hypertension on equine estrogens. In such cases, the transdermal route (patch, gel) should be favored, thereby primarily avoiding an overproduction of renin substrate [22].

2.2. Progestogens' mechanisms of action

The prevailing opinion with respect to oral contraceptives was that BP was mainly affected by the estrogen component, in other words, by ethinyl estradiol since progestin-only pills had little impact on BP. Very few studies though have specifically investigated how the various progestogens act on vessels that have previously been damaged. Since HRT is used in elderly women who exhibit a high incidence of arteriosclerotic lesions, like in the prematurely terminated WHI study, the progestin effects compared to OC may start to play a much more important role. Their action is particularly relevant with regard to BP as progestins can antagonize the vasodilative estrogen effects and even induce vasoconstrictive mechanisms. Additionally, several other unfavorable mechanisms have been demonstrated that take place in the metabolism and directly at the vessels, all of which can ultimately promote arteriosclerotic complications.

The actions of progestogens are thereby highly dependent on their pharmacokinetic properties, and this not only applies to the dose administered, but also to the concentration–time curve and particularly to the peak levels achieved. For example, Clarkson's group showed recently that medroxyprogesterone acetate (MPA) only antagonizes the beneficial effects of estrogen in terms of arteriosclerotic plaque inhibition in monkeys when given in a *single* daily dose. When distributed over *two* daily doses, the beneficial cardiovascular effects of estrogen are fully preserved [23]. The pharmacokinetic differences are particularly pronounced when the oral and transdermal routes are compared. In line with these findings, we were able to prove in postmenopausal women on treatment that oral progestin antagonized estrogen's vasodilative mechanisms, while estrogen's vasodilative effects were maintained after transdermal application (combi-patch) [24,25].

Similar to the unfavorable estrogen effects, the negative actions of progestins in general however are only to be attributed any clinical relevance when regulatory

systems are destroyed and/or prior vascular damage is present, for example as with arteriosclerotic lesions. Our own double-blind, placebo-controlled cross-over studies conducted first with postmenopausal women who had suffered a myocardial infarction and then on healthy women showed that the endothelial reserve in women with coronary heart disease is significantly impaired. Depending on the residual vascular function, this situation makes it extremely difficult for their bodies to defend themselves against vasoconstrictive effects [24,26]. By comparison, women without vascular lesions are able to react, e.g. with a rapid and significant release of vasodilative substances like nitric oxide and prostacyclin ([26–28], reviewed in Refs. [10,24]). This explains why the progestogen effects observed in studies have varied, and why experimental or epidemiological studies have often observed no negative progestogen effects in healthy women [29].

But also during treatment of hypertensive women special progestogens may not negatively interfere with blood-lowering estrogen effects, even positive, protective effects are possible considering specific effects of newer progestogens. Relevant to be mentioned in this review are antimineralocorticoid effects by interaction with the RAAS. Antimineralocorticoid effects have previously been demonstrated only for progesterone which use in HRT seems to be limited due to excessive metabolism with current available preparations. With the introduction of drospironone to oral contraception, which soon should be available also for HRT, it is possible to counteract specifically disorders associated with increased RAAS activity already demonstrated for symptoms of water retention which might be also of importance for treatment of hypertensive patients. Indeed, first placebo-controlled studies with estradiol/drospironone combinations show reductions in both systolic and diastolic BP, with evidence of a dose-dependency BP-lowering effect of drospironone, probably related to its aldosterone antagonism (A. Rübiger, data on file, personal communication). In addition further progestogens in development might elicit similar effects as discussed for example also for trimegestone although studies in hypertensive patients to our knowledge are not yet published.

To summarize, in light of the mechanisms of action—only discussed briefly in this context—we can expect that normotensive patients will not exhibit any or just minor progestogen effects that are

reflected by changes in BP. Conversely, these effects can become relevant in hypertensive patients or in those with pre-existing vascular diseases, whereby dose-dependency and the peak drug levels achieved may play the most important role.

2.3. Menopause status and blood pressure

Investigations into the potential effects of HRT on BP beg the essential question as to the extent that menopause status affects the BP. In fact, at least 15 longitudinal and cross-sectional studies have examined the association between age, menopause status and BP changes. After adjusting for age and body mass index, usually no significant correlation was found; in some studies, a marginally higher risk was noted; others observed a slight reduction in the risk of developing hypertension as a function of menopausal age.

Two studies can be cited as representative: in a study initiated by Casiglia et al. [30] in 1978, 408 premenopausal and 160 postmenopausal women were selected on the basis of a cross-sectional analysis (paired data). Over the course of the ensuing 16-year longitudinal study, they were not able to determine any difference between the groups with respect to BP changes after age-adjusted analysis.

The cross-sectional study conducted and analyzed by Amigoni et al. [31] included a very high number of patients. This study investigated the risk factors of 22,250 peri- and postmenopausal women in terms of the development of high BP. The following Odds Ratios (OR) were found (CI = 95% confidence interval): dependency of hypertension on age >61 years OR 2.7 (CI 2.5–2.9), BMI >25 kg/m² OR 2.7 (2.5–2.9), diabetes OR 2.0 (1.8–2.3), hypertriglyceridemia OR 1.9 (1.7–2.0). In other words, the major known risk factors for developing hypertension were confirmed. Over the course of the analysis, an OR of 1.6 (1.0–1.4) was found for the postmenopausal versus perimenopausal status—an almost significant risk. By contrast, the OR of women receiving HRT was 0.9 (0.8–1.0), in other words, almost a significantly lower risk. These data confirm de facto that this type of study only observes a marginal dependency of BP on endogenous or exogenous estrogens.

One can assume that the sudden withdrawal of endogenous estrogen by bilateral oophorectomy may lead to pressor effects of the menopause regardless

of age and body mass index. By surgery the woman is made menopausal immediately whilst the ‘natural menopause’ is a more gradual process. However, as far as longitudinal studies have investigated the effect of this “surgical menopause,” mostly similar results were achieved as for the effect of a “natural menopause,” i.e. that any difference disappeared after matching for age and BMI. Of more value regarding this topic are case/control studies. Thus a Finnish study demonstrated elevated blood pressures in women following oophorectomy compared with age-matched with ovaries still in situ [32]. Thus a pressor effect increasing BP induced by surgical menopause appears to be very possible, although up to now this has been investigated only in a few studies.

Generally it is assumed, based on observational studies, that cardiovascular risks occur especially after a sudden estrogen withdrawal, although prospective randomised trials are lacking on this topic. Results are probably coming from the analysis of the still ongoing WHI-study treating hysterectomized and partly ovariectomized women with estrogen-only therapy compared to placebo. Summarizing the present studies, the question whether BP increases independent of age following natural or surgical menopause has not yet been conclusively answered.

2.4. Studies on normotensive postmenopausal women

Having assumed that both oral contraception and HRT with ethinyl estradiol carry a potentially higher risk, the majority of studies were conducted on normotensive women, i.e. with BP values that were less than 140/90 mmHg before treatment, measured using a conventional Riva-Rocci sphygmomanometer (RR). Numerous studies of this type, frequently designed as case-control studies and mostly testing equine estrogens, date back to the 1960s and 1970s and most of them established no relevant effect of HRT (e.g. [32–36]). Later studies with improved methodology (with better adjustment of variables) also found no effect either (review in Ref. [37]), or when estradiol was used, e.g. in five studies conducted by Christiansen’s group [38], they tended to find slightly lowered BP. Several studies, however, did also register BP increases [5,39–46]. The methodological deficiencies in these studies must be addressed; for example in the

frequently quoted study by Persson et al. [47], 89% of the 23,233 women treated with estrogens were hypertensive prior to starting the study.

Evidence of drug-specific effects is found, among others, in a 9-month prospective comparative study on 160 primary normotensive postmenopausal women (average age 52 years) conducted by Wren and Routledge [41]. They observed a fall in BP with estrone sulfate which acts mainly by breaking down into estradiol. By contrast, conjugated equine estrogens (CEE) were associated with a marked elevation in BP which took place with doses of just 0.625 mg per day the elevation was >15 mmHg systolic in around 20% and >15 mmHg diastolic in approx. 10% of the women treated. Since the mixture of CEE contains a high percentage of estrone sulfate (approx. 50%), these negative effects can certainly be attributed to the equiline derivatives (30–40%) or to other animal components that do not naturally occur in humans. The increase in BP was not significant, when the average measurements were considered in terms of the whole sample; the risk observed on conjugated equine estrogens at the dose most frequently used in the age groups tested resulted exclusively from a subgroup that represented approx. 20% of the women. This indicates that a specific predisposing factor (disorder of RAAS?, see above) might be required.

This sort of elevated risk specifically on treatment with equine estrogens was not confirmed in the Postmenopausal Estrogen/Progestin Intervention (PEPI) study [48]. It is not possible to draw conclusions about *individual* risks, however, since this important study has unfortunately thus far only provided calculations of the mean, but no subgroup analyses or individual BP curves.

The PEPI study, which was conducted on healthy women, produced no evidence that the progestins MPA and progesterone used caused any negative effects on BP. In our own studies, we also tested various other progestogens that differed greatly with regard to their pharmacological properties. Altogether, we could not establish any relevant changes in BP. One of our studies on 416 women tested chlormadinone acetate (2 mg per day), a C21 gestagen with antiandrogen properties, and norethisterone acetate (1 mg per day), a C19 gestagen with androgen properties given in sequential combination (12 days/cycle) with transdermal estradiol (0.05 mg per day) [49]. No significant

effects were determined over the 4-month treatment. Likewise in combination with oral estradiol (2 mg per day), we found no negative BP effects in the various studies. We also tested different progestin doses, e.g. 0.5, 1.0, 2.0, 3.0 mg per day of chlormadinone acetate in a prospective randomized comparison on 159 postmenopausal women, without any effect on BP [50]. Likewise we were able to exclude any significantly relevant BP changes for dienogest, a C19 gestagen with antiandrogenic and other specific properties. We performed a prospective randomized comparison of 0.5, 1, 2, 3, and 4 mg dienogest continuously combined with estradiol treating postmenopausal women for 6 months [51,52]. We also randomly tested this combination versus estradiol monotherapy which would definitively have had to expose any potential effects of the progestin component if there were any [53].

These studies were carried out on healthy populations, although it can never be excluded that women with undetected illnesses or special predisposing factors were treated as well. Therefore, isolated reports about negative progestin effects occurring during the treatment of primarily normotensive women should not be all that surprising. The working group of Keneman reported on three prospective studies in which a total of 563 postmenopausal women were treated with micronized estradiol (2 mg), sequentially combined with various doses of dydrogesterone [54]. After 6 months' treatment a slight, but significant fall in systolic and diastolic BP was registered for the entire pooled group. After 1 year, however, the group receiving 10 mg per day dydrogesterone showed a significant rise in both systolic and diastolic BP of 2–3 mmHg. It has been well documented that dydrogesterone acts particularly neutral in terms of metabolic as well as of vascular effects when combined with 1 or 2 mg estradiol in dosages ranging from 5 to 20 mg per day [55–57]. However, exceptions also with well tolerated progestins might possibly be caused by certain patients with special dispositions that might not be detected since a causal relationship could be difficult to prove in the conventionally designed studies.

In the recent published prospective randomized 'Danish Osteoporosis Prevention Study' with 1,006 early postmenopausal women, Vestergaard et al. [58] also reported of three participants in whom HRT was terminated due to hypertension. In two of these,

borderline hypertension was present before initiation of HRT, in one patient BP increased only during HRT. However, in contrast to previous reports [5] there was no decrease of BP in connection with the termination of HRT. BP was normalized only after initiation of antihypertensive therapy (two patients) or after several years without antihypertensive medication, respectively. Thus causal relationship seems to be questionable but cannot be excluded.

Overall, these studies have shown that the risk of BP elevations on the various forms of HRT is low and that the likelihood of negative progestogen effects is slight. This also applies to the long-term regimens as established recently in the mentioned 'Danish Osteoporosis Prevention Study' [58], in which the HRT-group was treated with sequential estradiol/NETA (®Trisequenz, Novo Nordisk, Denmark) ($n = 407$) or with oral estradiol continuously (®Estrofem, Novo Nordisk, Denmark) ($n = 95$) and after 5 years of treatment with the exception of the three above mentioned cases with BP increases no negative influence on BP was observed, without significant differences between estrogen and estrogen/progestogen treatment. The Baltimore Longitudinal Study of Aging running since 1978 also confirms a good compliance under long-term treatment. Within 2–18 years of treatment (5.7 in the mean) this carefully evaluated cohort study on 226 primary normotensive women yielded no negative changes. Compared to the control group, "old-age" hypertension even tended to be prevented. In other words, a relatively minor increase in systolic BP was observed [59].

2.5. Studies on hypertensive postmenopausal women

Only relatively few studies are available in which BP measurements were intentionally taken in women with pre-existing hypertension. Essentially data is very sparse on the presumably most burning question: how might progestogens induce BP elevations in predisposed or at-risk women. Foidart found no significant BP changes in hypertensive women ($n = 92$) during 6 months' treatment with transdermal estradiol [60]. Likewise also Beljic et al. observed within 12 months ($n = 11$) no effect [61]. A study by Lip et al. on 75 women also showed no effect either [62], even though only patients were included who had documented BP

of $>160/95$ mmHg in at least two previous measurements (WHO criteria). Since various regimens were used, the number of patients in the individual subgroups was still rather low.

In contrast, diastolic and systolic BP were significantly reduced in the already cited Dutch study carried out by Keneman's group with estradiol/dydrogesterone on a subgroup of 99 hypertensive women [54]. In their studies comparing normotensive and hypertensive women ($n = 13/11$ and $12/12$, respectively) both Pines et al. [63] and Jespersen et al. [65] observed a reduction in BP in the hypertensive group only [64]. The routes of estradiol administration were sublingual and oral, respectively. Jespersen et al. [65] compared BP changes during estradiol only and during treatment with sequential estradiol/NETA. In normotensive women no significant changes were seen. In the hypertensive women systolic blood pressure fell significantly during treatment with estradiol as well as with sequential estradiol/NETA, while diastolic pressure did not change. Recently Fenkci et al. found no detrimental metabolic and vascular effects treating diabetic and hypertensive high risk patients with transdermal estradiol in a 3 months' case-control study (20/21)—BP did not change significantly [66].

According to our research, the first prospective, randomized, placebo-controlled study on postmenopausal hypertensive women was published by Luotola [67]. Using a cross-over design, the author documented a significant reduction in diastolic and systolic BP in both normotensive ($n = 20$) and hypertensive patients ($n = 20$) after 4 weeks' treatment with micronized estradiol at a dose of 2 mg per day. The reduction in BP was more pronounced in the hypertensive women.

By contrast, Kornhauser et al. did not observe any such changes in their prospective, double-blind, placebo-controlled study in which 55 moderately hypertensive women received monthly estradiol injections (10 mg, i.m.) for a period of 3 months [68]. Using the same study design, Modena et al. demonstrated a significant reduction in left ventricular mass after 18 months treatment with transdermal estradiol (0.05 mg per day) plus sequential 2.5 mg per day NETA orally in 86 hypertensive women without significant changes in BP [69]. Similarly beneficial cardiovascular changes, but correlating with mild,

Table 1

Blood pressure in 13,910 normotensive and hypertensive climacteric women during transdermal estradiol treatment with and without progestin combination in a large-scaled prospective German study

BP	Week	Gr. 1	Gr. 2	Gr. 3	Gr. A
BP systolic	0	133 (16)	132 (16)	131 (16)	154 (16)
	8	132 (15)	130 (14)	130 (15)	147 (15)
BP diastolic	0	82 (10)	81 (10)	80 (9)	100 (6)
	8	80 (9)	80 (9)	80 (9)	91 (8)

Main groups for stratification of data: Gr. 1: transdermal estradiol continuously, without progestin addition ($n = 3.871$); Gr. 2: transdermal estradiol cyclically, without progestin addition ($n = 6.768$); Gr. 3: transdermal estradiol cyclically, sequentially combined with progestin (72% norethisterone acetate 1 mg per day) ($n = 3.271$). Subgroup A: climacteric women with known hypertension. BP diastolic >95 mmHg before start of study ($n = 1.397$). BP office blood pressure (with Riva-Rocci sphygmomanometer (mmHg)), mean values (standard deviation).

and on average significant reductions in BP, were observed in a double-blind, placebo-controlled study with equine estrogens (0.625 mg per day), partially combined with sequential MPA (10 mg per day), after 6 months' treatment. Here, only 19 hypertensive women were tested however [70].

In one of our own studies, we analyzed a large study population that included both normotensive and hypertensive women. Table 1 presents a summary of the results. In a prospective, comparative, open study 13,910 women were treated with cyclically or continuously administered transdermal estradiol (0.025, 0.05, and 0.1 mg per day). All women except those with hysterectomy also received sequential progestin (NETA 47.2%, MPA 23.8%, medrogestone 10.8%, CMA 2.0%, dydrogesterone 1.5%, etc.). The primary study end points included a documentation of side effects, such as skin tolerability in particular, but also systemic effects [71]. The 12,394 normotensive women were not observed to have (on average) significant changes in BP during an 8-week treatment regimen, and there was no statistical evidence of negative progestin effects. However, increase of BP was documented in 30 patients as "adverse events" (0.22%) whereby a causal connection with HRT could not be ruled out with certainty although no serious clinical incidences were reported.

For a subgroup of 1397 hypertensive women, all of whom had a diastolic pressure of >95 mmHg

before starting HRT, we calculated a mean fall in BP of systolic 7 mmHg and diastolic 9 mmHg; in 39% of these women we found a diastolic drop of more than 10 mmHg. Those decreases of BP should be real although a "regression to the mean effect" could not be excluded in this non-randomized study.

2.6. Studies with 24-h blood pressure measurements

The results of studies published over the past years that evaluated the effect of HRT on BP based on 24 h ambulatory measurements are particularly meaningful. In Table 2 [72–81] and Table 3 [82–90], these results are listed separately for normotensive and hypertensive postmenopausal women. Remarkably, the majority of the studies, i.e. 13 of 19, used an estradiol patch [72–74,78–82,84–87,89], presumably because the lowest risk for an increase in BP was expected by the transdermal route. Eleven of the 13 studies conducted with estradiol patch showed significant reductions in BP, nine of them had a prospective, randomized placebo-controlled design with 24 h ambulatory BP measurements.

The studies on primary hypertensive women were carried out particularly carefully (Table 3). With three exceptions, they followed a placebo-controlled and cross-over design. Three studies tested parallel, albeit placebo-controlled groups [82,86,90]. Only the study by Landgren's group [86] did not show reduction in BP with the patch; the 24 h BP measurements did not demonstrate any significant effect before the study and at 12 months follow-up for oral and transdermal HRT. To our knowledge this study is, at the same time, the longest study conducted using this method, which examined elderly women (with an average age of 60 years) who had pre-existing coronary heart disease exclusively (50% post myocardial infarction). It can be speculated that the reduction in BP possibly achieved during long-term estrogen treatment is cancelled out by opposing mechanisms of action.

Four of the 11 studies that tested oral estrogen products alone [75–77,83,88,90] or in addition to transdermal application [72,73,79,81,86] showed a BP-lowering effect [73,75–77]. Comparatively speaking, the potential for a reduction in BP thereby appears to be more pronounced in women treated with transdermal HRT. In a recent study in hypertensive patients with conjugated equine estrogens (CEE)

Table 2
Prospective comparative studies with 24-h ambulatory BP measurements in normotensive postmenopausal women

Study	ET/EPT preparation (mg/die) (n)		Control (n)	Duration	BP decrease*		Mean BP decrease (mmHg)**	
					Systolic	Diastolic	Systolic	Diastolic
Akkad et al. [72]	ET	Patch 0.05 (40)	No	3/6 months	No/yes, N	Yes, D, N/yes, D, N	No/4.2 N	3.3 D, 3.8 N/4.0 D, 4.4 N
Cacciatore et al. [73]	sEPT	®Hormonin (oral) (50)	No	3/6 months	No/no	No/no	No/no	No/no ^a
		E2/NETA 0.05/0.25 Patch (35)	No	2/6 months	Yes, D/no	Yes, D/no	4.0 D/no	3.5 D/no ^b
Cagnacci et al. [74]	ET	E2/NETA 2/1 oral seq. (38)	No	2/6 months	Yes, D/yes, D	Yes, D/no	3.8 D/3.6 D	1.8 D/no
		Patch 0.05	Plac.	2 months	Yes, N	Yes, N	4.5 N	4.1 N
Christ et al. [75]	ET	Cross-over (18)	Control (23)	>6 months	Yes, D	Yes, D	8.0 D	5.2 D ^c
		E2 (17)		>6 months	No	No	No	No
Harvey et al. [76]	ET	E2/progestin oral (22)	Plac.	1 month	Yes, N (RR–)	Yes, N (RR–)	5.0 N	4.0 N ^d
		E1S oral 0.625		1 month	No (RR–)	Yes, N (RR–)	No	2.0 N
		E1S oral 2.5		1 month	Yes, N (RR–)	Yes, N (RR+)	4.0 N	4.0 N
		EE oral 0.02		1 month	Yes, N (RR–)	Yes, N (RR+)	4.0 N	4.0 N
Van Ittersum et al. [77]	sEPT	Cross-over (22)	Control (15)	12 months	Yes (RR–)	Yes (RR–)	8.9	5.9 ^e
		E2 oral 1 mg/DG 5/10 seq. (14)		2 months	Yes, N (D)	Yes, N (D)	6.0 N	5.0 N
Seely et al. [78]	ET	Patch 0.1	Plac.	2 months	Yes, N (D)	Yes, N (D)	8.0 N	2.0 N ^f
		Patch 0.2/Prog. 300 vaginal		10 weeks	Yes, N	Yes, N	8.0 N	2.0 N ^f
Vongpatanasin et al. [79]	ET	Cross-over (15)	Plac.	2 months	Yes, D	Yes, D	2.0 D	3.0 D ^g
		Patch 0.2		2 months	No	No	No	No
		CEE 0.625		2 months	No	No	No	No
WHILA-study [81]	ET	Cross-over (12)	Control (32)	24h	No (D, N)	No (D, N)	No	No ^h
		Patch (4)		24h	No (D, N)	No (D, N)	No	No ^h
		Patch (10)/oral (4)		24h	No (D, N)	No (D, N)	No	No ^h
Zacharieva et al. [80]	cEPT	Oral (14)	Control (25)	3 months	Yes, D, N (RR–)	No (RR–)	4.8 D, 3.1 N	No ⁱ
ET	Patch 0.05 (16)							

ET estrogen only therapy; EPT estrogen/progestogen therapy (sequential sEPT, continuous combined cEPT). BP: 24 h-ambulatory BP; RR office blood pressure (with Riva-Rocci sphygmomanometer). D: BP during day (15min measurements); N: BP during night (30min measurements), patch: transdermal E2. E2, estradiol; E1S, estronesulfate; EE, ethinylestradiol; CEE, conj. equine estrogens; NETA, Norethisterone acetate; MPA, medroxyprogesterone acetate; Prog, progesterone, DG, dydrogesterone.

* Significant decrease of mean BP compared to placebo or control group, in studies without control compared to basal values. No increase of mean BP was observed.

** Listed only significant changes, compared to placebo or control. No: no significant mean BP changes.

^a ®Hormonin (Shire Pharmaceuticals Ltd., Andover, Hants, UK): Estradiol 0.6 + Estriol 0.27 + Estrone 1.4 pro tablet; non-randomized comparison with patch.

^b BP evaluation only during progestogen phases.

^c BP evaluation during estrogen only compared to sEPT: progestin addition completely antagonized E2-induced decrease of BP as well as specific functional cardiac parameters.

^d Dose-dependent increase of plasma renin substrate, decrease in plasma renin concentration. However, no change in plasma renin activity or plasma aldosterone concentration.

^e BP evaluation only during estrogen phases; mean values without D/N-differentiation.

^f BP evaluation during estrogen and estrogen/progestogen phases: addition of progesterone (2 weeks) induced activation of renin-angiotensin-aldosterone system but resulted in no effect on BP. Significant decrease of night time BP, trend of decrease for day time BP.

^g Decrease of BP and decrease of sympathetic activity during transdermal E2; no effect during CEE.

^h Randomized case-control study within cross-sectional study ($n = 10.766$). No details regarding BP measurements during estrogen and estrogen/progestogen phases.

ⁱ Increase of prostaglandine E2 and vascular endothelial growth factor suggest vasodilatory effects; no change in active renin levels.

Table 3

Prospective, randomized placebo-controlled studies with 24-h ambulatory BP measurements in hypertensive postmenopausal women^a

Study	ET/EPT preparation (mg/die) (n)		Control (n)	Duration	BP decrease*		Mean BP decrease (mmHg)**	
					Systolic	Diastolic	Systolic	Diastolic
Affinito et al. [82]	sEPT	Patch 0.05/MPA (10) seq. (25)	Plac. (27)	6 months	Yes, D (RR–)	Yes, D (RR–)	5.5 D	5.7 D ^a
Harvey et al. [83]	sEPT	CEE 0.3/0.625/1.25 + MPA 10 seq. Cross-over (14)	Plac.	1 month	No, D, N	No, D, N	No	No ^b
Manhem et al. [84]	ET	Patch 0.1 Cross-over (13)	Plac.	24 h	No	Yes, D	No 0	3.0 D
Mercurio et al. [85]	ET	Patch 0.1 Cross-over (16)	Plac.	36 h	Yes, D, N	Yes, D	9.0 D, 9.0 N	5.0D
Tripp et al. [86]	sEPT	Patch 0.05; MPA 5 seq. (20) CEE 0.625; MPA 5 seq. (20)	Plac. (21)	12 months	No, D, N No, D, N	No, D, N No, D, N	No	No ^c
Rosano et al. [87]	ET	Patch 0.05 Cross-over (12)	Plac.	1 month	Yes, D, N	Yes, D, N	NA	NA
Sands et al. [88]	ET	Hormonin (oral) Cross-over (20)	Plac.	2 months	No, D, N	No, D, N	No	No ^d
Brito-Zurita et al. [90]	ET	CEE 0.625 (16)	Plac.	4 months	No, D, N	No, D, N	No	No ^e
Zoncu et al. [89]	ET	Patch 0.1 Cross-over (18)	Plac.	36 h	Yes, D, N	Yes, D	9.0 D, 11.0 N	5.0 D

ET estrogen only therapy; sEPT sequential estrogen/progestogen therapy, BP: 24-h ambulatory BP; RR office blood pressure (with Riva-Rocci sphygmomanometer), D: BP during day (15min measurements); N: BP during night (30 min measurements), patch: transdermal estradiol. CEE, conj. equine estrogens; MPA, medroxyprogesterone acetate.

* Significant decrease of mean BP compared to placebo. No increase of mean BP was observed.

** Listed only significant changes, compared to placebo. No: no significant mean BP changes; NA: no answer, missing values.

^a BP evaluation during estrogen and estrogen/progestogen phases: no significant differences between phases.

^b BP evaluation only during progestogen phases. Study was not blinded in terms of sequential MPA addition. Variable effects during CEE/MPA, BP situation worsened with higher doses of equine estrogens.

^c All patients with pre-existing coronary heart disease and hypertension. No details comparing BP in estrogen and estrogen/progestogen phases.

^d ®Hormonin (Shire Pharmaceuticals Ltd., Andover, Hants, UK): Estradiol 0.6 + Estriol 0.27 + Estrone 1.4 pro tablet.

^e Compared to baseline significant decrease of diastolic BP during CEE and placebo. However, decrease was larger during placebo causing significant higher values of diastolic BP during CEE when compared to placebo after 4 months' study.

0.625 mg per day after 4 months' therapy significant higher values of diastolic BP compared to placebo were seen although diastolic BP relative to baseline was decreased in both groups [90]. One study [83] with CEE observed variable BP effects: With 0.3, 0.625, or 1.25 mg per day there was no effect demonstrated by the 24-h measurements (BP); when the measurements were performed with the Riva-Rocci sphygmomanometer (RR) patients receiving 0.3 mg showed mean reductions in both systolic and diastolic BP; only diastolic reductions were found with 0.625 mg per day, and no effects with 1.25 mg per day, i.e. the BP situation worsened with higher doses of equine estrogens. These results are noteworthy since they were obtained in trials with a cross-over design, i.e. with the same (hypertensive) women.

In their recent study, Christ et al. [75] showed that the BP situation worsened when progestins were added: estradiol showed an improvement in computer-measured cardiovascular parameters such as heart rate variability (as a parameter reflecting autonomic tone), and reductions in systolic and diastolic BP were demonstrated by the 24 h measurements. However, when oral progestins such as NETA, medrogestone, levonorgestrel or MPA were added, all of these beneficial effects were antagonized. This interesting study was notably not conducted placebo-controlled and used different HRT preparations and thereby had correspondingly small subgroups. It therefore cannot be ruled out that the higher risk related to progestin applied to isolated women with a specific constellation of factors. Altogether, all studies available thus far, even those using 24 h measurements, provide little information about the potential effects of progestins.

It is noteworthy that normotensive women receiving treatment with estrogen particularly showed reductions in nocturnal BP. In contrast, it was shown that daytime BP was reduced more frequently in the hypertensive women (i.e. mostly receiving concomitant antihypertensive treatment). However, there is still too little evidence on this subject and the results are too varied for definitive conclusions to be made. Likewise a current evaluation as to whether HRT has a stronger effect on systolic or diastolic BP is not possible as the available data appear too controversial to allow an evaluation. Frequently, a reduction in both values is observed.

2.7. Lacking data from interventional studies

The available evidence allows the conclusion that overall the risk for an increase of BP is low with all forms of HRT. Therefore, this type of hormonal effect would only lead to clinical sequelae such as heart attack and stroke in exceptional cases. Now, the question must be asked whether such suspicious cases were observed in the recent placebo-controlled interventional studies which followed the primary study objective of determining such clinical cardiovascular endpoints.

As mentioned at the beginning, particularly the negative results from the prematurely stopped WHI study re-ignited discussions about a re-evaluation of cardiovascular risks including hypertension, also on the part of the authorities. It seems remarkable indeed that 36% of the women tested in the WHI who had BP values above 140/90 mmHg were treated with antihypertensive drugs. Despite this, an increase in systolic BP "by an average of 1.5 mmHg and more" was already seen within the first 2 trial years on HRT when compared with placebo [6]. These increases are substantial in terms of mean values in large study populations, particularly considering the high drop-out rate of over 40% in the WHI, since these values statistically otherwise tend to decline (regression to the mean effect). The authors did not explain the increases in BP found in the WHI study and it is still unclear as to what extent greater increases in BP occurred in isolated women who might then have also statistically contributed to the clinical complications like cerebral stroke that were observed.

It would also have been very valuable to have such information on the study population of the Heart and Estrogen/Progestin study (HERS) since a defined high-risk sample was investigated—to our knowledge, however, no such data are available. Notably, no such information is contained in the first original publication [91], not even for the subsequent subgroup analyses aimed at ascertaining individual risks [92] nor in the follow up study (HERS II) [93].

Comparably meager to completely lacking is the information about BP profiles and correlations with a cardiovascular risk from the other recently published interventional studies, in which a prospective,

randomized and placebo-controlled design was used to determine the effects of HRT on cardiovascular risks such as heart attack and stroke (PHASE, WHISP, ESPRIT, and WEST), or on surrogate end points such as angiographic measurements and the intima media thickness (ERA, EPAT, PHOREA, and WAVE) (reviewed, e.g. in Ref. [94]). This would have been helpful to make correlations. So, it must be said that the chances offered by new, major studies have not been utilized to properly mine the data indicative of blood pressure increase, the most important risk factor for cardiovascular diseases.

3. Conclusion

Regulation of BP is always first on the list of all pertinent recommendations, like those given by the “American Heart Association” with respect to key measures for preventing cardiovascular diseases such as heart attack and stroke [95]. Like patients taking oral contraceptives, the BP of women receiving HRT should be monitored very closely, such monitoring is mandatory in patients with at high risk of cardiovascular disease.

Nonetheless, a negative effect involving increases in BP should only be expected in rare exceptions. It is still unclear as to the nature of the predisposition that must exist for this to happen. When hypertension is present, treatment with physiological estradiol should be recommended. In general, the lowest possible doses should be given, and particularly with regard to the progestogen. Since increases in BP were observed extremely rarely in the studies reviewed, rather more reductions were observed, and notwithstanding the need for monitoring of individual patients, the data available do not justify listing hypertension as a contraindication in the form that is currently being contemplated by some national health authorities.

However, as recent interventional studies have shown, an elevation of cardiovascular risks cannot be ruled out. Thus, every treatment involving hormone replacement should be properly indicated by strict diagnostics. This particularly applies to hypertensive women, as they frequently show arteriosclerotic morbidities which would increase the cardiovascular risk during HRT.

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