Advances in hormone replacement therapy with drospirenone, a unique progestogen with aldosterone receptor antagonism

Santiago Palacios⁎⁎, Jean-Michel Foidart⁎, Andrea R. Genazzani⁎

⁎ Instituto Palacios, Salud y Medicina de la Mujer, Madrid, Spain
⁎ Department of Obstetrics, Gynecology and Senology at the University of Liege, Belgium
⁎ Department of Obstetrics and Gynecology, University of Pisa, Italy

Abstract

Unlike other currently available progestogens, drospirenone (DRSP) has a pharmacological profile, which closely mimics that of endogenous progesterone, most notably potent anti-aldosterone and anti-androgenic effects. Consequently, DRSP, when combined with 17β-estradiol (E2) as hormone replacement therapy (HRT), offsets E2-related water and sodium retention by blocking the mineralocorticoid receptor. This review evaluates the potential benefits offered by DRSP as the progestin component of HRT with respect to its anti-aldosterone activity, which translates into positive effects on body weight and blood pressure in clinical trials of continuous, combined E2/DRSP in post-menopausal women. In a 1-year, large-scale, randomised, controlled trial, E2 1 mg/DRSP 2 mg significantly decreased mean body weight by 1.2 kg versus baseline (P < 0.001), whereas patients receiving E2 1 mg gained weight. E2 1 mg/DRSP 2 mg also significantly lowered mean systolic blood pressure (SBP) by 9.0 mmHg from baseline (P < 0.05) versus 3.7 mmHg in the E2 1 mg group (P = 0.220) in a sub-group of hypertensive women. In addition, E2/DRSP was not associated with hyperkalemia (potassium ≥ 5.5 meq/L) irrespective of concomitant use of ACE inhibitors, angiotensin II receptor antagonists or non-steroidal anti-inflammatory drugs, and co-morbid diabetes mellitus. In summary, as well as effectively treating climacteric symptoms, DRSP 2 mg combined with E2 1 mg has shown positive effects on body weight and blood pressure in clinical trials, most likely due to DRSP's anti-aldosterone properties. This combination may therefore offer an alternative therapeutic option with additional benefits beyond current HRT agents for symptomatic post-menopausal women.

Keywords: Progestogen; Hormone replacement therapy; Drospirenone; Post-menopausal women; Hypertension

1. Introduction

It is estimated that 47 million women per annum will be menopausal by 2030 [1], and approximately 80% of these women will experience transient or permanent symptoms, related to the loss of estrogens, during the menopause stages [2]. The transient menopausal symptoms can be vasomotor in origin, i.e. hot flushes, night sweats or palpitations, or psychological, such as insomnia. Permanent symptoms include urogenital atrophy and osteoporosis.

For decades, estrogen, either alone or in combination with progestogens, has been the therapy of choice for the relief of menopausal symptoms, as well as for the long-term prevention of post-menopausal osteoporosis. The inclusion of a progestogen in continuous combined hormone replacement therapy (HRT) decreases the risks of endometrial hyperplasia and cancer associated with unopposed estrogen therapy, and this approach eliminates regular withdrawal bleeding [3,4]. Evidence-based guidelines strongly recommend the use of combined estrogen/progestin therapy in women with an intact uterus, using the lowest dose to relieve symptoms effectively and minimise side-effects [5-9]. However, the potential benefits of HRT on cardiovascular disease, blood pressure and weight gain remain controversial, and may depend on the specific regimen used.

Post-menopausal women have a higher prevalence of hypertension than pre-menopausal women [10-12], and are consequently at an increased risk of cardiovascular disease. High blood pressure is a modifiable risk factor, as reductions can lower the incidence of stroke and coronary heart disease (CHD). Even lowering the blood pressure in pre-hypertensive individuals (systolic blood pressure [SBP] 120-139 mmHg or diastolic blood pressure [DBP] 80-89 mmHg) may have an added health benefit [13]. Treatment with conventional HRT appeared to have no significant effect on blood pressure in a number of studies [13-18]. The risk of hypertension was increased in current HRT users in the WHI study, although this may have been related in part to the older
patient cohort in this study (average 62 years) [12]. In some patients, blood pressure may increase due to the water- and sodium-retaining effects of the estrogen in HRT preparations, mediated via the renin-angiotensin-aldosterone system (RAAS) [19].

Weight changes can occur independently of the menopause, although adverse weight changes in body fat distribution and composition are linked to hormonal changes [20]. It is widely perceived that HRT causes weight gain [21,22], although data from clinical trials examining weight gain is inconclusive, in some studies showing an increase in overall body weight [15,23-25] and others showing no significant effect [26-32]. It is possible that differences in measures of weight gain, physical activity of responders, HRT regimens (e.g. the use of micronized progesterone), may account for the differences observed in these trials. Some studies indicate that HRT may have positive effects on body fat distribution [25,28-32], for example, data from the Post-menopausal Estrogen/Progestin Interventions (PEPI) trial showed that HRT may reduce central adiposity [32], although the current evidence is inconclusive [26].

Nevertheless, weight gain is perceived as a side-effect and is commonly cited as a reason for not taking HRT [21,22,33,34]. The Norwegian Woman and Cancer (NOWAC) study, which sampled 4996 women (1024 HRT users that experienced side-effects were identified) aged 45-64 years, showed that 56.3% of women experiencing troublesome side-effects reported weight gain as a side-effect [33]. Similar findings were observed in another large-scale survey of 816 women (449 responders). This study showed that concerns about weight gain were associated with a significant risk (RR = 2.06) for discontinuing HRT [34]. In contrast to endogenous progesterone, the currently available synthetic progestogens lack anti-aldosterone activity. This may result in HRT-associated water retention and bloating as a consequence of estrogen activity on the RAAS, which could contribute to perceived weight gain. This highlights the need for progestogenic compounds that mimic the effects of endogenous progesterone on the RAAS. Drospirenone (DRSP) is a novel progestogen with aldosterone receptor antagonism (PARA). In contrast with most synthetic progestogens, DRSP displays a very similar pharmacological profile to endogenous progesterone [35-37]. Thus, DRSP exhibits anti-aldosterone and anti-androgenic properties, but is devoid of any estrogenic, glucocorticoid or anti-glucocorticoid activity [35,36,38-40]. In particular, the anti-aldosterone activity of DRSP provides the potential for positive effects on body weight and also on blood pressure due to counterbalancing estrogen-related water retention when used in an HRT preparation. Several studies have demonstrated the safety and efficacy of the continuous combined HRT, 17β-estradiol (E2) 1 mg and DRSP 2 mg (Angeliq®, Schering AG, Germany) for the treatment of climacteric symptoms and prevention of post-menopausal osteoporosis [41-43]. In this review, the function of the RAAS, and in particular the effects of estrogen and progesterone, on body weight and blood pressure are discussed. The potentially advantageous effects of E2 1 mg/DRSP 2 mg on body weight and blood pressure in post-menopausal women are also evaluated. Due to its unique potent anti-aldosterone activity, DRSP in combination with E2, could offer an alternative HRT with a favourable benefit/risk ratio for post-menopausal women.

2. The influence of estrogen and progesterone on the RAAS

The RAAS plays a key role in the regulation of body fluids and blood pressure. If there is a sustained fall in blood pressure, the kidney releases renin, which converts angiotensinogen to angiotensin I (Fig. 1). This inactive peptide is subsequently converted by angiotensin-converting enzyme (ACE) to the pharmacologically active angiotensin II. Angiotensin II in turn stimulates aldosterone secretion, resulting in conservation of sodium and water, and elimination of potassium by the kidney [40,44]. In addition, angiotensin II is a potent vasoconstrictor, causing acute elevations in blood pressure. The most important function of the RAAS is to prevent excessive sodium loss and to regulate blood pressure. In addition, aldosterone may be implicated in the pathogenesis of renal and cardiovascular disease.

The female sex hormones, estrogen and progesterone are both known to influence the RAAS. Endogenous and orally administered estrogens promote the synthesis of angiotensinogen, leading to increased plasma aldosterone levels via the RAAS [19,44]. The net physiological effect of unopposed estrogen is increased sodium and water retention, and decreased potassium retention. In the natural menstrual cycle, progesterone counteracts the endogenous estrogen-induced stimulation of the RAAS by competing with aldosterone at the mineralocorticoid receptor [44]. Ideally, synthetic progestogens should be capable of fulfilling this role in women treated with exogenous estrogens.
3. DRSP: a synthetic progestogen with added benefits

Progestogenic activity is essential in HRT preparations to counteract the proliferative effects of estrogen on the uterine endometrium. However, endogenous progesterone has low oral bioavailability and a short plasma half-life, rendering the hormone unsuitable for use in HRT preparations [45,46]. Although micronized progesterone is available for use in HRT, and data, for example, from the PEPI trial demonstrated that it is effective [18], most HRT combinations contain a synthetic progestogen, commonly derived from 19-nortestosterone (e.g. norethisterone acetate [NETA]) or 17α-hydroxyprogesterone (e.g. medroxyprogesterone acetate [MPA]) [46-48]. While all conventional progestogens exert progestogenic activity, they exhibit different patterns of binding at other steroid receptors and consequently display diverse biological activities (Table 1) [40,46-48], which also prevent meaningful extrapolation of the results for one progestogen to all progestogens as a class, or indeed to all HRT preparations.

Table 1: Comparison of the biological activities of progesterone and drospirenone with other progestogens

<table>
<thead>
<tr>
<th>Progestogens</th>
<th>Biological activities</th>
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<tr>
<td></td>
<td>Progestogenic</td>
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<tr>
<td>Progesterone</td>
<td>+</td>
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<tr>
<td>Drospirenone</td>
<td>+</td>
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<tr>
<td>Cyproterone acetate</td>
<td>+</td>
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<tr>
<td>Dienogest</td>
<td>+</td>
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<tr>
<td>Levonorgestrel</td>
<td>+</td>
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<tr>
<td>Medroxyprogesterone acetate</td>
<td>+</td>
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<tr>
<td>Norethisterone</td>
<td>+</td>
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<tr>
<td>Trimegestone</td>
<td>+</td>
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<tr>
<td>Norgestimate</td>
<td>+</td>
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</tbody>
</table>

Clinically relevant activity (+); activity not clinically relevant (±); no activity (-).
None of the progestogens currently used in conventional HRT preparations has a similar pharmacologic profile to that of progesterone, most notably with regard to their lack of anti-mineralocorticoid activity (Table 1). They are, therefore, unable to adequately counterbalance the water- and sodium-retaining effects of the estrogenic component of combined HRT, which may contribute to increased blood pressure and weight gain in susceptible individuals. As such, there is clearly an unmet clinical need for new, well-tolerated progestogenic compounds with improved selectivity that mimic the effects of endogenous progesterone [47].

DRSP (6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone), differs from conventional progestogens as it is derived from 17α-spiroloctane, rather than progesterone, 19-nortestosterone or 19-norprogesterone [46,47]. The novel chemical structure of DRSP underpins its unique receptor binding profile among synthetic progestogens. Moreover, its binding region and biological activities are closely akin to those of endogenous progesterone (Table 1) [35,36,40]. DRSP and progesterone both exhibit moderate binding affinity to progesterone receptors and high binding affinity to mineralocorticoid receptors (as antagonists) in the uterus and kidney [45]. Both DRSP and progesterone have considerable anti-mineralocorticoid activity in transactivation studies of hormone receptors [35,38]. The anti-androgenic potency of DRSP is reported to be 5-10 times greater than that of progesterone and one-third that of cyproterone acetate (CPA). This contrasts with the absence of anti-androgenic activity for MPA [40,45]. Neither DRSP nor natural progesterone display estrogenic, androgenic or glucocorticoid activity [44,45,47]. Unlike other progestogens, DRSP has anti-aldosterone activity. The binding affinity of DRSP at the mineralocorticoid receptor is 2.3- to 5-fold higher than that of aldosterone, whereas the affinity of MPA or NETA is only approximately 3% that of aldosterone, and neither display anti-mineralocorticoid activity [45,47]. In spontaneously hypertensive rats, SBP and DBP were decreased or remained unchanged over 27 days of DRSP administration, whereas blood pressure increased with conventional progestogens, such as CPA [45]. In addition, DRSP has been shown to increase sodium excretion compared with placebo or CPA in menstruating women [44]. Like progesterone, DRSP therefore has the potential to counter the increase in sodium and water retention caused by estrogenic stimulation of the RAAS, which may otherwise result in increased plasma volume, water retention-related symptoms and raised blood pressure in susceptible individuals. Thus, in contrast with conventional progestogens, the unique PARA activity of DRSP may offer beneficial effects on blood pressure and body weight in post-menopausal women. The ratio of pro-gestogenic to anti-mineralocorticoid activity is similar for DRSP and progesterone [44], and DRSP is the only available progestogen that has significant anti-aldosterone activity at dose levels sufficient to oppose the effects of E2 on the endometrium. DRSP in combination with E2 has, therefore, been developed as a continuous combined HRT, as well as an oral contraceptive with ethinyl estradiol (EE).

4. The effect of DRSP on blood pressure

Hypertension, defined by the JNC VII guidelines [13] as stage 1: SBP 140-159 mmHg or DBP 90-99 mmHg; stage 2: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, is linked to cardiovascular disease [49-51], a leading cause of death in the western world [52]. In the Framingham Heart Study, a longitudinal 30-year survey, which examined data from normotensive and untreated hypertensive subjects, SBP increased linearly with age; if left untreated, elevated SBP can accelerate large artery stiffness, an independent determinant of cardiovascular risk [51].

Age-related conditions such as the menopause can also have an impact on blood pressure. In a random cross-sectional survey of households where blood pressure was measured on-site, data from 278 premenopausal women and 184 post-menopausal women showed that the latter group was associated with a higher incidence of hypertension (≥140/90 mmHg), which was still evident after adjusting for age and body mass index (BMI) [10]. Although blood pressure measurements were home-based, these results may still be subject to the white-coat effect, which is more relevant in small samples. Another larger survey, which reviewed 15 longitudinal and cross-sectional studies, found that after adjusting for age and BMI, no significant correlation was found between menopause and blood pressure. However, this paper did not state whether these subjects were normotensive or hypertensive at baseline, or whether they were receiving HRT or anti-hypertensive therapy [53].

The link between post-menopausal estrogen deficiency, hypertension and subsequent risk of cardiovascular disease, therefore, remains somewhat unclear. A review of blood pressure changes in hypertensive post-menopausal women receiving conventional HRT agents has revealed a variety of effects, although in general, risks of increased blood pressure during therapy were low [13-18,53]. A small, observational study of 226 normotensive post-menopausal women showed that HRT users had a smaller increase in SBP than non-users over the 5-6 year follow-up (change in SBP: 8.9 mmHg versus 1.6 mmHg; P = 0.01) [17]. However, one cannot rule out the possibility of a natural ageing effect, such as that observed in the Framingham Heart Study [51],
given the absence of a control group or defined endpoints. A number of well-designed trials (see Table 2) have consistently demonstrated a significant blood pressure-lowering effect with DRSP plus E2 in postmenopausal women [43,54-56]. This is consistent with the potent anti-aldosterone activity of DRSP. In one study, 24 postmenopausal hypertensive women treated with enalapril (baseline blood pressure: 139/82 mmHg) were randomised to treatment with E2 1 mg/DRSP 3 mg once daily or placebo plus enalapril for 14 days. Blood pressure was measured by 24 h ambulatory monitoring. E2/DRSP significantly reduced 24 h mean (+S.E.) SBP by 9 mmHg (+1.4) and DBP by 5 mmHg (+1.2) from baseline (both \(P<0.05\)), whereas no change in blood pressure was observed in the placebo plus enalapril group [54]. These findings show that E2/DRSP has added benefits on blood pressure when used in combination with other anti-hypertensive agents.

### Table 2: Summary of trials demonstrating the blood pressure-lowering effects of DRSP

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>BP definition(s)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preston et al.</td>
<td>Post-menopausal women (n = 24)</td>
<td>14-day, double-blind, randomised, parallel-group study</td>
<td>24 h ambulatory BP (no HTN criteria used)</td>
<td>Significant additive BP-lowering effect of E2/DRSP (mean decrease from 139/80 to 130/75 mmHg), consistent with anti-mineralocorticoid effect</td>
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<tr>
<td>[54]</td>
<td>treated with E2/DRSP/ENA or PLA/ENA</td>
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<tr>
<td>Preston et al.</td>
<td>Post-menopausal women with T2D (n = 82) or without T2D (n = 148) treated with E2/DRSP or PLA</td>
<td>28-day, randomised, PLA-controlled, multicentre study</td>
<td>Changes in clinic BP (no definition of HTN but baseline BP was 132/81 mmHg)</td>
<td>Higher BP reductions for E2/DRSP than PLA (mean reduction in total group: -8.6/-5.8 to -3.7/-2.9 mmHg; (P&lt;0.01)). No difference in hyperkalemia ((K\geq 5.5) meq/L) between treatment groups</td>
</tr>
<tr>
<td>[55]</td>
<td>treated with E2/DRSP or PLA</td>
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<tr>
<td>White et al.</td>
<td>Post-menopausal women with stage 1 HTN (n = 213) treated with E2/DRSP or PLA</td>
<td>12-week, multicentre, double-blind, PLA-controlled</td>
<td>Stage 1 HTN defined as SBP 140-159 and/or DBP 90-99 mmHg. Endpoints were changes in clinic BP and 24 h ambulatory BP</td>
<td>Mean clinic BP reductions for E2/DRSP vs. PLA were -14.1/-7.9 and -7.1/-4.3 mmHg ((P&lt;0.0001)). Significant reductions in mean 24 h SBP were also observed after treatment with E2/DRSP ((P = 0.002))</td>
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<tr>
<td>[56]</td>
<td>treated with continuous E2 with/without DRSP (5 regimens in total)</td>
<td>Multicentre, double-blind, randomised, parallel-group study (13, 28-day treatment cycles)</td>
<td>Endometrial hyperplasia (primary endpoint); BP (secondary endpoint)</td>
<td>The probability of hyperplasia was 0.060 for the E2 group compared with 0.007 for E2/DRSP 2mg. Significant reduction in mean BP after treatment with E2/DRSP 2 mg vs. E2 (-9.0/-5.7 mmHg vs. -3.7/-2.7 mmHg)</td>
</tr>
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</table>

BP, blood pressure; DBP, diastolic blood pressure; DRSP, drospirenone; E2, 17β-estradiol; ENA, enalapril maleate; HTN, hypertension; PLA, placebo; SBP, systolic blood pressure; T2D, Type 2 diabetes mellitus.

In a larger study, 230 post-menopausal hypertensive women treated with anti-hypertensive therapy (baseline blood pressure: 132/80 mmHg) were randomised to treatment with E2 1 mg/DRSP 3 mg or placebo for 28 days [55]. The mean decrease in clinic SBP from baseline was greater for E2/DRSP than placebo (-9.62 ± 1.30 and -2.78 ± 1.02 mmHg, respectively; \(P<0.001\)) (Fig. 2A). Corresponding values for DBP were -5.74 mmHg (+0.72) and -2.94 mmHg (+0.65), respectively (\(P<0.01\)) (Fig. 2B). A similar trend was observed in a sub-group of patients with type 2 diabetes mellitus.

In post-menopausal women with untreated stage 1 hypertension (SBP 140-159 mmHg; DBP 90-99 mmHg), treatment with E2 1 mg/DRSP 3 mg decreased both clinic and 24 h ambulatory blood pressure compared with
placebo after 12 weeks of therapy [56]. The mean clinic blood pressure was decreased by 14.1/7.9 mmHg (SBP/DBP) from baseline in patients receiving E2/DRSP compared with only 7.1/4.3 mmHg in the placebo group ($P<0.0001$). These findings show that the combination of E2 1 mg/DRSP 3 mg has a significant effect on blood pressure in untreated hypertensive patients and an additive effect in patients treated with anti-hypertensives. The reductions observed in the placebo group of these trials are consistent with previous findings and were not due to any lifestyle interventions. The placebo effect is a well-recognised phenomenon in blood pressure trials, and is usually more evident with clinic measures than 24 h ambulatory monitoring [57]. In a long-term trial, which evaluated the safety of E2 1 mg and four regimens of E2 1 mg/DRSP (0.5, 1, 2 or 3 mg) in 1147 post-menopausal women, the combination of E2/DRSP was effective in protecting against endometrial hyperplasia [43]. Secondary endpoints included, amongst others, blood pressure assessments. Based on a post hoc analysis in 102 hypertensive women (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg), there was a significant decrease in mean SBP from baseline in those receiving E2 1 mg/DRSP 2mg (−9.0 mmHg; $P = 0.011$; $n = 15$) whereas the decrease from baseline was not significant with E2 monotherapy (−3.7 mmHg; $P = 0.220$; $n = 15$) after 13, 28-day treatment cycles. Similarly, the mean DBP change from baseline in the E2/DRSP group was -5.7 mmHg ($P<0.001$) compared with -2.7 mmHg in the E2 monotherapy group ($P = 0.108$), although inter-treatment comparisons did not reach significance. While this study also demonstrated a beneficial effect of E2/DRSP on total cholesterol and low-density lipoprotein cholesterol, there was no actual assessment of cardiovascular endpoints such as stroke, CHD or myocardial infarction. Long-term studies are needed to address the effect of E2/DRSP on cardiovascular outcomes in order to determine whether the observed reduction of blood pressure has implications for these serious risks.

Nevertheless, these findings show that E2/DRSP consistently lowers blood pressure, which is most likely related to the anti-aldosterone activity of DRSP; aldosterone blockade increases renal sodium excretion, potentially leading to a reduction in SBP and DBP. Concomitant with the increase in sodium excretion via the RAAS, aldosterone receptor antagonists may also increase serum potassium concentrations, particularly in susceptible individuals [19,37]. However, E2/DRSP has not been associated with hyperkalemia (potassium ≥ 5.5 meq/L), even in high-risk patients [43,55,56]. When compared with placebo, treatment with E2 1 mg/DRSP 3 mg did not
increase serum potassium concentrations or the incidence of hyperkalaemia, irrespective of concomitant use of ACE inhibitors, angiotensin II receptors antagonists or nonsteroidal anti-inflammatory drugs, and co-morbid diabetes mellitus [55]. In addition, there were no clinically or statistically significant changes in serum potassium concentrations in patients with mild renal impairment and normal renal function when treated with DRSP or placebo [55].

Overall, E2 1 mg/DRSP 2 or 3 mg lowered SBP by approximately 7-14 mmHg and DBP by approximately 5-8 mmHg in hypertensive post-menopausal women in these trials. Although these changes may appear small, decreases in SBP of only 2-3 mmHg have previously been associated with improved cardiovascular outcomes [58-60]. Mean reductions in SBP and DBP of 10 and 4 mmHg, respectively, have been shown to decrease the risks of stroke and myocardial infarction by 30% and 23% [58]. There is also evidence to suggest that across the blood pressure range 115/75-115 mmHg, the risk of cardiovascular disease doubles with each increment of 20/10 mmHg in individuals aged 40-70 years [61]. These findings underscore the importance of even small decreases in blood pressure, and concur with recommendations to lower blood pressure by lifestyle changes even in pre-hypertensive individuals (i.e. SBP 120-139 mmHg or DBP 80-89 mmHg), as they are twice as likely to develop hypertension than individuals with lower blood pressures [13]. As yet, however, there are no data indicating that E2 1 mg/DRSP 2 mg has a role in reducing the risk of stroke or CHD in post-menopausal women with elevated blood pressure.

5. The effect of DRSP on body weight

Although women tend to gain weight after the menopause, regardless of whether or not they are prescribed HRT, particular concern among patients about weight gain during HRT can deter initiation of treatment and cause poor compliance and/or early discontinuation among users [21,22,33,34]. For instance, one quarter of former HRT users aged 45-75 years cited weight gain as a reason to discontinue therapy in a European study of 8012 women [22].

As mentioned above, DRSP is a potent aldosterone antagonist that acts on the mineralocorticoid receptor to decrease sodium reabsorption and water retention. The potential benefits offered by this improved pharmacological profile of DRSP have translated into a positive effect on body weight in clinical trials of an oral contraceptive containing DRSP and EE [62-64] (see Table 3). Data from two large, randomised, comparative trials show that mean body weight remained significantly lower in women receiving the oral contraceptive EE 30 µg/DRSP 3 mg than in women receiving EE 30 µg/desogestrel 150 µg over 13 or 26 cycles [63,64].

Similar findings have been shown when E2/DRSP is used as HRT in post-menopausal women [43]. In one trial (see Table 2), post-menopausal women receiving E2 1 mg/DRSP 2 mg experienced a small decrease in body weight, whereas women receiving E2 1 mg monotherapy tended to gain weight, even after the first treatment cycle (Fig. 3) [43]. At study end (cycle 13), the mean difference between treatments was 0.9 kg (P< 0.001), with women in the E2/DRSP group losing a mean of 1.2 kg versus baseline over the study period (P< 0.001). These results suggest that DRSP 2 mg, when used in a combined continuous HRT treatment with E2, has a body weight-lowering effect in post-menopausal women. This favourable effect likely reflects the unique ability of DRSP to counteract estrogen-related water and sodium retention, whereas conventional progestogens are devoid of such anti-mineralocorticoid activity.

Fig. 3. Change in body weight (mean±S.E.) in post-menopausal women receiving HRT with E2 1 mg/DRSP 2 mg or E2 1 mg for 13 cycles. *P< 0.001 vs. E2 monotherapy. DRSP, drospirenone; E2, 17β-estradiol; HRT, hormone replacement therapy; SBP, systolic blood pressure [43].


### Table 3: Summary of trials showing the beneficial effects of DSP on weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Weight assessment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oelkers et al. [62]</td>
<td>Healthy women ($n = 80$), aged 18-34 years, treated with EE/DRSP or levonorgestrel (control)</td>
<td>6-month, randomised trial (6 treatment cycles)</td>
<td>Body weight measured by women on home scales every second day (unclothed, fasting states). Mean weights during a cycle were used for calculations</td>
<td>Body weight reductions ranging from 0.8 to 1.7 kg in the DRSP/EE groups compared with an increase in the control group of 0.7 kg ($P &lt; 0.05$; DRSP/EE groups vs. control)</td>
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<tr>
<td>Foidart et al. [63]</td>
<td>Healthy women ($n = 900$), aged 18-35 years, treated with EE/DRSP or EE/desogestrel</td>
<td>Randomised, open-label, multicentre study (26 treatment cycles; 3-month follow-up)</td>
<td>Body weight measured by women on home scales (unclothed, fasting states). Weight checked weekly. Mean weights during a cycle were used for calculations. Mean pre-treatment weight was baseline</td>
<td>In the DRSP/EE group, the mean body weight remained below baseline (-0.11 to -0.68 kg). In the EE/desogestrel group, there was an increase after cycle 5 (range: +0.02 to +0.89 kg)</td>
</tr>
<tr>
<td>Huber et al. [64]</td>
<td>Healthy women ($n = 2069$), aged 18-35 years, treated with EE/DRSP or EE/desogestrel</td>
<td>Randomised, open-label, multicentre study (13 treatment cycles)</td>
<td>Body weight measured by women on home scales (unclothed, fasting states). Mean weights during a cycle were used for calculations</td>
<td>Weight loss was significantly greater in the EE/DRSP group than EE/desogestrel (-0.46 vs. -0.19 kg; $P &lt; 0.0072$)</td>
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</table>

### 6. Conclusions

DRSP has a pharmacodynamic profile that is more similar to that of endogenous progesterone than other currently available synthetic progestogens. When administered with E2 1 mg, DRSP 2 mg is an effective and well-tolerated HRT for the treatment of climacteric symptoms and prevention of post-menopausal osteoporosis. Due to the unique anti-aldosterone activity of DRSP, E2 1 mg/DRSP 2 mg also confers a positive effect on body weight and blood pressure in post-menopausal women. By avoiding estrogen-related side-effects such as bloating and weight gain, E2 1 mg/DRSP 2 mg may improve compliance with HRT, which is important in order to achieve maximum treatment benefits such as effective symptom relief and protection against osteoporosis. In addition, by reducing blood pressure in post-menopausal women, E2 1 mg/DRSP 2 mg may offer additional health benefits to women potentially at risk of later cardiovascular disease, although this has yet to be directly evaluated in clinical trials. In summary, the novel properties of DRSP, in combination with E2, provide an alternative therapeutic option with additional benefits beyond current HRT agents.

### Acknowledgement

This work was supported by Schering AG.

### References


[34] Reynolds RF, Obermeyer CM, Walker AM, Guilbert D. The role of treatment intentions and concerns about side effects in women's decision to discontinue postmenopausal hormone therapy. Maturitas 2002;43:183-94.


