Effects of continuous-combined oral drospirenone-estradiol on blood pressure, body weight & lipid profile in early menopausal women

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Background & objectives: Drospirenone (DRSP) is a progestin with antimineralocorticoid and anti-androgenic activity. When administered in combination with estradiol (E2), it relieves menopausal symptoms. The aim of this study was to evaluate the effects of DRSP/E2 on the reduction of cardiovascular risk factors in menopausal women with hypertension.

Methods: A retrospective study was conducted at the Clinical Center of Serbia. The participants were 64 menopausal women [mean age=49.19±4.62 yr, mean body mass index (BMI)=25.08±2.94 kg/m², mean amenorrhoeic period=2.48±2.46 yr]. The effects of DRSP 2 mg/E2 1 mg on 24 h blood pressure (BP) variability, heart rate (HR), anthropometric characteristics and hormone and lipid levels were evaluated in early menopausal women with previously untreated stage 1 hypertension. All analyses were carried out before and after six and 12 months of therapy.

Results: DRSP/E2 significantly reduced daytime BP values during six and 12 months of therapy. The reductions in systolic and diastolic BPs ranged from about −4.50 to −8.50 and from −4.00 to −5.00 mmHg, respectively. There were no significant changes in nocturnal 24 h BPs. DRSP/E2 significantly reduced HR daytime and night-time during the follow up period. DRSP/E2 significantly lowered the BMI, concentrations of total cholesterol, low-density lipoprotein cholesterol and apolipoprotein B, while high-density lipoprotein cholesterol and apolipoprotein concentration increased.

Interpretation & conclusions: Continuous long-term therapy with DRSP 2 mg/E2 1 mg significantly lowered 24 h systolic and diastolic BPs and reduced the risk of cardiovascular disease in early menopausal women with stage 1 hypertension. Timely initiated menopausal hormone therapy can have beneficial effects on BP and can reduce the incidence of cardiovascular disease in menopausal women.

Key words Cardiovascular disease - drospirenone - hormone therapy - hypertension - menopause

During menopause, the decrease in estrogen production increases blood pressure (BP) through multiple mechanisms: an increase in sympathetic activity, oxidative stress, abdominal obesity,
hyperinsulinism or reduced elasticity of the arteries\textsuperscript{1}. Hypoestrogenism induces hyperaldosteronism, endothelial dysfunction, autonomic neurological dysfunction, ventricular arrhythmias, sodium retention and potassium loss, leading to increasing prothrombotic activity, myocardial fibrosis and necrosis\textsuperscript{2}. In the period of climacterium and menopause, estrogen deficiency reduces the elasticity of the blood vessel wall and promotes development of arterial hypertension. This increases the risk of developing cardiovascular disease\textsuperscript{3}. Rahman \textit{et al}\textsuperscript{4} have shown that early natural menopause (40–45 yr) increases cardiac pathology by 40 per cent. Consequently, estrogen replacement may prevent the onset of hypertension during menopause. Results of some randomized controlled trials with the conventional menopausal hormone therapy (MHT) show that there is no difference regarding the group of progestogens and time of initiation of MHT on the effects of MHT on cardiovascular system\textsuperscript{5,6}.

Hormone therapy based on the use of estrogen in combination with progesterone, known as oral contraceptive therapy in addition to contraception, is also used in the treatment of polycystic ovary syndrome as well as a hormone therapy in menopause (MHT)\textsuperscript{7}. Depending on the indication and in order to individualize the therapy, there are different combinations of estrogens (17\textbeta-estradiol (E2), ethinyl-estradiol and diethylstilboestrol) and progestogens (derivatives of C21 and C19 steroids) in the market. Furthermore, there are different dosage forms available as well. In menopause, hormone therapy uses as substitution therapy, because the missing hormones are compensated. However, estrogen and progesterone cause thromboembolism and are known to have adverse effects on lipid and glycaemic profile which might complicate MHT. To change the biological activity in order to avoid adverse effects, modifications of the chemical structures of various estrogens and progesterones are performed. Although a low dose of 17\textbeta-estradiol (E2) may be combined with both progestogens and progestins, these may antagonize some estrogenic effects also none of these have antimineralocorticoid activity\textsuperscript{8}.

Drospirenone (DRSP) is a progestin derived from 17\textalpha-spironolactone. DRSP has antialdosterone and antiandrogen effects\textsuperscript{9}. When administered in combination with 17\textbeta-estradiol (E2), DRSP can be used as an effective hormone therapy for menopausal women\textsuperscript{10}. Previous clinical studies showed that the combination of DRSP and E2 was effective in protecting against endometrial hyperplasia and in relieving menopausal symptoms\textsuperscript{10,11}. The beneficial effects of DRSP/E2 on menopausal hypertension include a reduction in extracellular water and body weight\textsuperscript{12}, the protection of endothelial function and lower concentrations of total cholesterol, triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C)\textsuperscript{13,14}. Used separately, as the only drug, DRSP/E2 has an antihypertensive effect\textsuperscript{15} and also has additive interactions with standard antihypertensive drugs\textsuperscript{16}. This suggests that DRSP/E2 might be used as adjuvant antihypertensive therapy, especially in otherwise healthy early menopausal women where classical antihypertensive therapy may be insufficient. DRSP may cause hyperkalaemia, which is a consequence of its antialdosterone properties. According to some studies, even the highest dose of 3 mg DRSP does not cause an increase in hyperkalaemia in healthy and hypertensive postmenopausal women\textsuperscript{10,17}.

The point of our research is to indicate that adequate selection of estrogen and progestogen and in adequate dose in menopausal women can prevent and/or decrease the increase in BP and negative changes in lipid and metabolic status, which happen in menopause. So far, published evidence suggests that DRSP/E2 has an antihypertensive effect in menopausal women\textsuperscript{15,17,18}. However, some data regarding these effects are inconsistent. Based on the evidence showing that the initiation of MHT early in menopause prevents any BP increase later in life\textsuperscript{19,20} and taking into account the effects of DRSP/E2 on some cardiovascular risk factors\textsuperscript{9,12,22}, the present study had two objectives. The first was to determine whether the combination of DRSP 2 mg/E2 1 mg affects the 24 h BP and heart rate (HR) early in the menopausal women with stage I hypertension previously untreated with antihypertensive medications. The second was to evaluate the effects of DSRP/E2 on anthropometric characteristics along with hormone and lipid levels.

**Material & Methods**

\textit{Patients}: The study included 64 women in menopause [mean age=49.19 yr, standard deviation (SD)=4.62]. The sample size for a study was calculated using software (G\textsuperscript{*}Power version 3.1.9.2, Germany; by Franz Faul, Universität Kiel, Germany). The sample size depended on the statistical test used, type of power analysis and input parameters such as tails, effect size, \( \alpha \) error probability, 1–\( \beta \) error probability, number of
groups, number of measuring and SD. The calculated total sample size was 42-63 participants, which provided the actual study power from 0.81 to 0.97.

**Inclusion criteria:** Untreated menopausal women with their meant seated clinic systolic BPs ranging from 130 to 139 mmHg and/or diastolic BPs ranging from 80 to 89 mmHg stage 1 hypertension. Untreated condition meant all patients who had not been previously treated with any antihypertensive drugs. Menopause was defined as an amenorrheic period greater than one year with serum follicle-stimulating hormone (FSH) values >40 IU/l in women older than 45 yr of age. All included women were in their early menopause and had reported various menopausal symptoms such as hot flushes and sweating, depressive mood sleep disturbances and vaginal dryness.

**Exclusion criteria:** Uterine bleeding of unknown aetiology, carcinomas of any organ, pregnancy, liver or kidney failure, porphyria, malignant hypertension in multiple step therapy with antihypertensives, recent myocardial infarction or unstable angina, congestive heart failure, thromboembolism, previous administration of hormonal (estrogen or progestin) therapy in menopause, body mass index (BMI) >30 kg/m², concomitant medications including antihypertensives, potassium supplements, potassium-sparing diuretics, anticoagulants (heparin or warfarin), antiarrhythmic agents and a serum potassium level >5.0 mmol/l.

**Study design:** This was a retrospective and clinical interventional study conducted at a tertiary care gynaecological endocrine centre of the Clinic for Endocrinology, Diabetes and Metabolism, Clinical Center of Serbia, Belgrade, Serbia, in partnership with the department of Pharmacology, Faculty of Medicine, Belgrade, Serbia, and the departments of Biochemistry and Pathology, School of Dental Medicine in Belgrade, Serbia. The study was conducted from December 2018 to June 2019 and included women who were treated between March 1996 and November 2010 with the approval from the Local Ethical Committee, Belgrade. The patients received DRSP 2 mg with E2 1 mg once a day every morning. The therapy lasted for 12 months, without a break. The treatment group was followed up for 12 months. The general data in the protocol included the name and surname, age, age of menarche and menopause, duration of newly discovered hypertension in menopause and antihypertensive therapy. The measurements performed included 24 h ambulatory monitoring of BP and HR, anthropometric characteristics, hormonal status and lipid profile. All measurements were determined before and after six and 12 months of therapy. Between these three evaluations, comparisons were performed.

**Measurements of blood pressure (BP) and heart rate (HR):** The ambulatory BP and HR monitoring were performed with the ABPM-902071q apparatus (Spacelabs Healthcare, USA) according to the standard protocol. The BP cuff was placed on the non-dominant arm. BP measurement was recorded automatically every 15 min during 24 h. While recording the BP, the patient’s arm was immobilized. Vigorous physical activity and showering were not allowed.

**Anthropometric measurements:** BMI was calculated as the ratio of weight (kg) to the square of height (m). The waist-to-hip ratio (W/H) was calculated by dividing the waist circumference by the hip circumference. The waist circumference was measured at the umbilical level, while the hip circumference was measured at its greatest gluteal protuberance.

**Laboratory assessments of hormonal and lipid status:** Venous blood samples were collected from patients at 8.00 AM after an overnight fasting. The serum samples were examined to obtain hormonal and lipid parameters. All icteric or haemolytic blood samples were discarded. Hormonal status was assessed by determining the values of FSH (IU/l), luteinizing hormone (LH) (IU/l), estradiol (E2) (pmol/l), progesterone (P) (nmol/l), total testosterone (T) (nmol/l), sex hormone-binding globulin (SHBG) (nmol/l), dehydroepiandrosterone sulphate (μmol/l), prolactin (PRL) (mIU/l) and thyroid-stimulating hormone (TSH) (mIU/l). The serum concentrations of hormones were detected by radioimmunoassay methods using commercial kits (Sigma-Aldrich, St. Louis, MO, USA). The lipid metabolic profile, included total cholesterol (mmol/l), high-density lipoprotein cholesterol (HDL-C) (mmol/l), LDL-C (mmol/l), TGs (mmol/l), lipoprotein a [Lp(a)] (g/l) and apolipoprotein A and B (Apo-A and Apo-B) (g/l). Lp(a), Apo-A and Apo-B specify additional nephelometry methods (Nephelometer, BN/100, Behring, Germany). Total cholesterol, LDL, HDL and TG levels were determined by means of chromatography methods (Cobas 6000, Hitachi, Roche Diagnostics, Tokyo, Japan).

**Statistical analyses:** Depending on the type of variable
and the normality of the distribution, the data were presented as mean±SD and median (Q1-Q3). To test the data with repeated measurements one-way analysis of variance (one-ANOVA) was used with repeated measurements, Friedman and Wilcoxon lambda test. A P value lower than 0.05 was considered statistically significant.

**Results**

*Patient characteristics:* The present study included 64 menopausal women receiving DRSP 2 mg/E2 1 mg. Their mean age was 49.19 yr (mean=49.19, SD=4.62). The mean age of the last menstrual cycle was 46.72 yr (mean=46.72, SD=4.27), and the mean amenorrhoea period was 2.48 yr (mean=2.48, SD=2.46). Most of the participants (73.4%) were smokers.

*Effects of drospirenone (DRSP)/E2 on blood pressure (BP) and heart rate (HR):* The characteristics of dynamic changes in 24 h systolic and diastolic BPs and HR are shown in Table I. DRSP/E2 therapy significantly decreased daytime BP in a time-depending manner. In comparison to the measurements obtained before the initiation of the treatment, after six and 12 months of therapy, the mean systolic BPs reduced within the mean range of −4.50, SD=1.96 to −8.50, SD=3.41, and −4.00, SD=1.44, to −5.00, SD=2.39, respectively. The most significant decrease in systolic and diastolic BPs was observed 4-10 h after administering DRSP/E2. No significant changes in nocturnal BP were detected during follow up period. There were significant changes in HR during day and night.

**Effects of drospirenone (DRSP)/E2 on daytime blood pressure (BP) values during 12 months of therapy:** The results of the Friedman test showed that there was a significant difference \[C²(N=64)=38.21; P<0.05\] in the results of systolic BP values during the day obtained in the follow up periods (before therapy, six and 12 months after the introduction of therapy, respectively). The median values showed a decrease in the value of upper BP during the daytime period before the introduction of therapy (median=129), six months after the introduction of therapy (median=125) as well as a decrease in 12 months after the introduction of therapy (median=121) (Table I). The results of the Friedman test showed that there was a significant difference \[C²(N=64)=31.42; P<0.05\] between the diastolic BP values during the day obtained in three time periods (before therapy, six and 12 months after the introduction of therapy). Compare to the before the introduction of therapy (median=84), there were a decrease in the value of the lower BP during the daytime six months (median=80) and 12 months (median=79) after the introduction of therapy (Table I).

**Effects of drospirenone (DRSP)/E2 on night-time blood pressure (BP) values during 12 months of therapy:** There was no significant difference \[C² (N=64)=0.56; P>0.05\] in the results of systolic BP values during the night obtained in follow up periods (before therapy, six months and 12 months after the introduction of therapy, respectively). Similarly there was no significance in the value of diastolic BP either (Table I). There was also no significant difference \[C² (N=64)=0.82; P>0.05\] in the diastolic BP values during the night obtained in follow up periods.

| Study parameters | 50th (median) | n | P |
|------------------|---------------|---|---|
| **Systolic BP/day** |               |   |   |
| Before MHT       | 129.00        | 64 | <0.05* |
| Six months after MHT | 125.00      |     | |
| 12 months after MHT | 121.00      |     | |
| **Diastolic BP/day** |             |   |   |
| Before MHT       | 84.00         | 64 | <0.05** |
| Six months after MHT | 80.00       |     | |
| 12 months after MHT | 79.00       |     | |
| **Systolic BP/night** |           |   |   |
| Before MHT       | 104.00        | 64 | >0.05 |
| Six months after MHT | 106.00      |     | |
| 12 months after MHT | 106.00      |     | |
| **Diastolic BP/night** |          |   |   |
| Before MHT       | 66.00         | 64 | >0.05 |
| Six months after MHT | 63.00       |     | |
| 12 months after MHT | 62.00       |     | |
| **HR/day** |               |   |   |
| Before MHT       | 76.00         | 64 | <0.05* |
| Six months after MHT | 72.00      |     | |
| 12 months after MHT | 72.00      |     | |
| **HR/night** |              |   |   |
| Before MHT       | 68.00         | 64 | <0.05** |
| Six months after MHT | 62.00      |     | |
| 12 months after MHT | 60.00       |     | |

*Friedman test: C² (n=64)=38.21; P<0.05; **Friedman test: C² (n=64)=31.42; P<0.05; *Friedman test: C² (n=64)=12.90; P<0.05; "Friedman test: C² (n=64)=7.54; P<0.05. The results are presented as median mmHg or HR. MHT, menopausal hormone therapy; BP, blood pressure; HR, heart rate
up periods. The median values did not show a decrease in the value of systolic BP during the night-time in either of the three time points.

Effects of drospirenone (DRSP)/E2 on heart rate (HR) values during 12 months of therapy: The median values showed a decrease in HR during the day across all three time points (Table I). At night, there was a significant difference \(C^2(N=64)=7.54; P<0.05\) in the results of HR values obtained at the three time points which showed a decrease (Table I).

Effects of drospirenone (DRSP)/E2 on anthropometric characteristics: Table II shows that MHT with DRSP/E2 after 12 months of follow up was not caused significant changes in BMI and W/H ratio in menopausal women. A one-way ANOVA with repeated measure showed no significant difference \(P>0.05\) between BMI before (mean=25.00 kg/m², SD=2.90) and 12 months after therapy (mean=25.15 kg/m², SD=2.58) and also there was no significant difference \(P>0.05\) between W/H ratio before (mean=0.79, SD=0.06) and 12 months after the therapy (mean=0.78, SD=0.41).

Effects of drospirenone (DRSP)/E2 on hormonal status: The changes of hormone levels are shown as mean±SD in Table III. As expected, MHT increased serum concentrations of estradiol and SHBG while the concentrations of FSH, LH and DHEA decreased. A one-way ANOVA with repeated measure showed a significant difference \(P<0.05\) between the levels of SHBG, FSH and DHEA before six and 12 months after the therapy, while there were no significant changes in the levels of progesterone, testosterone, PRL and TSH levels during DRSP/E2 therapy compared to the values obtained before the initiation of the therapy.

Effects of drospirenone (DRSP)/E2 on lipid profile: All values of lipid profile are presented in Table IV. Before initiating DRSP/E2, higher values of total cholesterol (mean=6.33, SD=1.29) and LDL-C (mean=4.29, SD=1.09) were found. A one-way ANOVA of repeated measure found that the use of MHT with DRSP/E2 resulted in a significant \(P<0.05\) decrease in total cholesterol and HDL values and increase in HDL values after six and 12 months from the start of therapy. The results of the Friedman test \(C^2(N=62)=68.66\) show

### Table II. Anthropometric characteristics of patients (body mass index and waist-to-hip ratio) before and 12 months after menopausal hormone therapy

| Study parameters | BMI | W/H |
|------------------|-----|-----|
|                  | Mean±SD | P | Mean±SD | P |
| Before MHT       | 25.00±2.90 | >0.05* | 0.79±0.06 | >0.05** |
| During 12 months MHT | 25.15±2.58 | 0.78±0.41 |

*Wilcoxon lambda=0.98; \(P>0.05\); \(\text{Wilcoxon lambda}=0.71; P>0.05\). BMI and W/H are represented as mean±SD. BMI, body mass index; W/H, waist-to-hip ratio; SD, standard deviation

### Table III. Effects of drospirenone/estradiol on hormonal levels during the 12 months of therapy

| Hormone       | Before MHT | Six months of MHT | 12 months of MHT | \(P\)    |
|---------------|------------|-------------------|------------------|---------|
| FSH (IU/l)    | 74.22±27.69| 32.15±13.93       | 27.69±12.54      | <0.05*  |
| LH (IU/l)     | 32.90±19.37| 18.98±11.45       | 16.32±10.98      | <0.05** |
| E2 (pmol/l)   | 12.87±7.37 | 79.18±55.22       | 101.33±50.31     | <0.05***|
| Progesterone (nmol/l) | 3.20±0.71 | 2.91±0.75         | 2.72±0.89        | >0.05   |
| Testosterone total (nmol/l) | 2.23±0.75 | 0.92±0.46         | 2.13±0.72        | >0.05   |
| DHEAS (μmol/l) | 2.80±1.52 | 2.27±1.13         | 1.88±0.93        | <0.05a  |
| SHBG (nmol/l) | 45.47±17.06| 62.08±22.90       | 71.85±31.31      | <0.05aw |
| Prolactin (mIU/l) | 234.76±87.40| 248.71±120.81     | 227.50±87.41     | >0.05   |
| TSH (mIU/l)   | 2.23±0.75 | 2.27±0.74         | 2.13±0.72        | >0.05   |

*Wilcoxon lambda=0.17; \(P<0.05\); \(\text{Wilcoxon lambda}=0.21; P<0.05\); \(\text{Wilcoxon lambda}=0.37; P<0.05\); \(\text{Wilcoxon lambda}=0.51; P<0.05\); \(\text{Wilcoxon lambda}=0.47; P<0.05\). Each number represents the mean±SD of the hormonal values. MHT, menopausal hormone therapy; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; SD, standard deviation
that there was a significant ($P<0.05$) difference in the values of Apo-A obtained during the follow up periods. Median value of Apo-A showed a significant increase during the follow up period. Before the introduction of therapy, the median was 1.48, six months after the introduction of therapy was 1.67 and at 12 months, it was 1.81. Compared the values of Apo-B of patients with menopausal hypertension obtained before (median=1.35), six (median=1.20) and 12 months (median=1.04) of the beginning treatment showed a significant decrease during the follow up period.

**Discussion**

The main finding of this study was that the administration of DRSP (2 mg) in combination with E2 (1 mg) without other antihypertensive drugs effectively reduced both systolic and diastolic 24 h BPs in women in early menopause who are diagnosed with stage-1 hypertension. Another important finding of this study was that administering DRSP (2 mg) and E2 (1 mg) did not induce clinically significant changes in body weight in overweight women with stage-1 hypertension. DRSP/E2 significantly decreased total cholesterol and LDL-C levels. Nevertheless, it increased HDL-C levels, which indicated that it might contribute to reducing the cardiovascular risk. To the best of our knowledge, in Serbia, so fare there was no report about investigation of DRSP/E2 on hypertension and lipid profile in menopausal women. Although this drug has been in the market for a long time, the results of post-marketing surveillance in different countries are always a value addition. Furthermore, despite the numerous results, DRSP/E2 is not widely used in the treatment of menopausal hypertension.

The antihypertensive effect of DRSP/E2 observed in our study is in agreement with previous findings. However, some of the results are not consistent. This could be due to the different methods of BP measurement, the dose of DRSP and E2, the duration of therapy, monitoring other parameters related to the efficiency and safety of the therapy, the duration of menopause, the presence of comorbidity and the concomitant use of another therapy. The present study included women at the onset of menopause since another study conducted on a group of hypertensive menopausal women showed that approximately 40 per cent of them had developed arterial hypertension during the climacteric period in the early years of menopause. Furthermore, menopausal women with stage 1 hypertension were included because one of the aims was to reduce hypertension at its onset. Although it is known that DRSP/E2 can potentiate the antihypertensive effect of angiotensin-converting enzyme inhibitors such as enalapril, our results showed that when administered as the only drug, it provides a higher degree of efficiency and safety when it comes to reducing hypertension. This is in concordance with previous reports. In comparison to using the sphygmomanometer for the clinical measurement of BP, 24 h Holter monitoring provides a more reliable antihypertensive assessment since there is a lack of observer bias, as well as the

**Table IV.** Effects of drospirenone/estradiol on lipid profile during the 12 months of therapy

| Study parameters | Before MHT | Six months of MHT | 12 months of MHT | $P$ |
|------------------|------------|-------------------|-----------------|-----|
| T-chol (mmol/l)  | 6.33±1.29  | 5.88±0.93         | 5.84±0.79       | <0.05* |
| HDL-C (mmol/l)   | 1.32±0.40  | 1.39±0.27         | 1.48±0.32       | <0.05** |
| LDL-C (mmol/l)   | 4.29±1.09  | 3.86±0.84         | 3.72±0.81       | <0.05*** |
| TG (mmol/l)      | 1.52±0.57  | 1.34±0.43         | 1.20±0.38       | >0.05 |
| Lp (a) (g/l)     | 0.11±0.21  | 0.11±0.21         | 0.10±0.18       | >0.05 |
| Apo-A (g/l)      | 1.48±1.76  | 1.67±1.81         | 1.81±2.00       | <0.05* |
| Apo-B (g/l)      | 1.35±0.32  | 1.20±0.26         | 1.04±0.30       | <0.05** |

*Wilcoxon lambda=0.89; $P<0.05$; **Wilcoxon lambda=0.6; $P<0.05$; $^c\chi^2$=68.66; $P<0.05$; ***Wilcoxon lambda=0.50; $P<0.05$. Each number represents the mean±SD of the lipid values, except Apo-A and Apo-B as median values. T-chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Lp (a), lipoprotein a; Apo-A, apolipoprotein A; Apo-B, apolipoprotein B.
increased number of values taken over the dosing interval, and the enhanced statistical reproducibility. Although DRSP has a mineralocorticoid receptor-blocking activity, potassium levels were not measured in this study. Many studies have shown low incidences of hyperkalaemia caused by DRSP/E2 compared with placebo. However, in specific patients with concomitant therapy predisposing to hyperkalaemia, blood monitoring is recommended to determine potassium levels. It should be noted that DRSP/E2 might be used as an adjuvant antihypertensive at low doses, as in our study, (DRSP 2 mg with E 1 mg) while for contraception use, a higher dose of DRSP 3 mg with E2 was used. This is especially important because of potassium, because with an increase in the dose of DRSP, there is a higher risk of hyperkalaemia. Although some studies have shown that DRSP 3 mg with E2 lowers BP without significant development of hyperkalaemia, lower doses should be preferred. In the last few years, it has been suggested that the use of MHT in primary prevention of coronary heart disease is proven beneficial when given appropriately in terms of doses of administration and types of hormones. The Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2019 has included DRSP/E2 as an option in regulation of menopausal hypertension, with monitoring of BP and adverse reactions.

Data suggests that DRSP/E2 compared to other MHTs has a more favourable effect on body weight. Furthermore, it is also suggested that DRSP/E2 therapy does not affect body weight from baseline. The present study did not show a decrease in BMI and W/H ratio in menopausal women after 6 and 12 months of therapy. If DRSP/E2 therapy does not reduce excessive body weight, it is important that it does not increase it since obesity is an additional risk factor for the development of cardiovascular disease. In the early menopausal period, women gain weight, without changing eating habits and calorie intake. While, the reasons are hyperinsulinism, hypo-estrogenism and hypoprolactinism, in addition, there are many other triggers leading to obesity in menopause, including leptin, adiponectin and cortisol with consequent metabolic syndrome and diabetes mellitus. Increase in weight gain depends on different modifiable and non-modifiable factors. Increase in weight gain of ≥3 per cent during the first three years in menopausal women up to 65 yr is associated with early menopause transition and an intentionally lost 10 or more kg during the past 20 yr. The aim of this study was not to follow up women during period longer than one year, but rather to study women with amenorrhoeic period prior to MHT of about 2.5 yr. All women, receiving hormone replacement therapy with estradiol and DRSP, did not gain weight, as it was expected in non-MHT users.

In this study DRSP/E2 significantly decreased total cholesterol and LDL values and increased HDL after six and 12 months of therapy, suggesting that DRSP/E2 may reduce the cardiovascular risk and mortality rate by changing the lipid profile. All parameters of lipid status represent a biomarker of the atherosclerotic process, especially LDL, which is a consequence of menopause, i.e. a decrease in estradiol levels. Several studies have shown some beneficial effects of DRSP/E2 on the lipid metabolism. Our results are in agreement with the previous reports suggesting a significant decrease of total cholesterol and LDL levels, but not when it comes to the an increase in HDL-C levels. Furthermore, the treatment with DRSP/E2 resulted in significantly decreased Apo-B and increased Apo-A levels at six and 12 months of therapy. However, data suggests that the Apo-B/Apo-A ratio was more correlated with postprandial TG/HDL-C in women and can be helpful in assessing metabolic risk. Although smoking belongs to a modifiable group of risk factors for cardiovascular disease and most people do not give up this habit easily, the high frequency of this habit requires that the therapy be effective even when this risk factor is present. Although 73 per cent of women in the present study were smokers, DRSP 2 mg/E2 1 mg preserved blood vessels from higher lipid levels and hypertension, and it happened during 2.5 amenorrhoeic menopausal years. Our results of DRSP/E2 on the lipid and metabolic biomarkers point out the importance of including MHT as a substitution therapy on time, at the onset of menopause, with the aim of reducing cardiovascular risk and consequently the mortality rate.

This study has some limitations. The patients were followed up before including therapy and after six and 12 months of therapy. After that, they were controlled by a general practitioner, gynaecologist and cardiologist. So, there is no information on how long they used DRSP/E2.

Overall, the results of this study show that estrogen-progestogen therapy with DRSP 2 mg/E2 1 mg is an effective hormone combined therapy that can be initiated in early menopause in patients with stage 1 hypertension in order to prevent cardiovascular disease and improve the quality of life.
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Conflicts of Interest: None.

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