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Angeliq versus Activelle in normotensive postmenopausal women: a prospective, randomized pilot study

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Abstract

Objective: The aim of this study was to compare, in normotensive postmenopausal women, the effects of drospirenone/estradiol and norethisterone acetate/estradiol on blood pressure and other surrogate markers of cerebrovascular and cardiovascular risk.

Methods: Thirty postmenopausal women were submitted to utero-ovarian ultrasonography and to color Doppler evaluation of ophthalmic arteries. Ultrasonographic and Doppler analysis of brachial artery flow-mediated vasodilatation and 24-hour ambulatory blood pressure monitoring were performed. Plasma concentrations of nitrites/nitrates were assayed. The participants were randomly assigned to drospirenone 2 mg/estradiol 1 mg (group 1; n = 15) or norethisterone acetate 0.5 mg/estradiol 1 mg (group 2; n = 15) treatment. The duration of the study was 6 months.

Results: The basal pulsatility index and the back pressure of the ophthalmic artery were similar in groups 1 and 2. After 6 months, no changes were observed. The nitrites/nitrates values were not different between groups 1 and 2 both in basal conditions and after therapy. The brachial artery flow-mediated vasodilatation and the pulsatility index of the brachial artery did not show any difference in groups 1 and 2 both in basal conditions and after the therapy. The 24-hour blood pressure monitoring showed no significant differences in the 24-hour time, daytime, and nighttime values either in basal conditions or after therapy. All participants were found to be dippers normally (nocturnal reduction ≥10% in comparison with diurnal values). The wake-up blood pressure values were similar in the studied participants.

Conclusions: A 6-month hormone therapy with drospirenone/estradiol or norethisterone acetate/estradiol is equally effective and does not seem to alter the surrogate markers of cardiovascular and cerebrovascular risk.

Key Words: Drospirenone – Norethisterone acetate – Hormone therapy – Menopause – Hypertension.

In postmenopausal women, the loss of ovarian function is associated with a high prevalence of hypertension and other important hemorrheological changes that may contribute to a dramatic increase in the incidence of ischemic heart disease and stroke.

Several observational studies have shown that hormone therapy (HT) reduces up to 50% the risk of cardiovascular and cerebrovascular diseases in postmenopausal women.[1,2] The HT benefits are believed to be mediated, to a large extent, through favorable changes in plasma lipid and lipoprotein profile. However, the HT-induced changes in plasma lipid and lipoprotein concentrations account for less than 50% of the reduction in cardiovascular mortality.[1,2] Several lines of evidence suggest that sex hormones have direct or mediated effects on vessel wall physiology, and receptors for estrogens have been found in the great vessels.[3-8] Furthermore, it is well known that estrogens may also positively influence atherosclerosis by acting on nitric oxide production, insulin sensitivity, proliferation and mitogenesis of vascular wall smooth cells, platelet aggregation, endothelin-1 and calcium-mediated vessel constriction, and basal coronary vasomotor tone and reactivity.[9] In addition, Pines et al[10,11] found that estrogens increase both stroke volume and cardiac contractility in healthy postmenopausal women. Moreover, it has been demonstrated that the physiological modifications mentioned above improve Doppler-derived central and peripheral hemodynamic parameters.[12-17]

Recently, large randomized prospective studies have refuted these protective effects and underlined that the risk of hypertension is increased in current HT users.[18,19] In some

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susceptible women, via the renin-angiotensin-aldosterone system (RAAS), blood pressure and body weight could increase because of the water- and sodium-retaining effects of estrogens.[20] Progesterone may counteract the estrogen-induced stimulation of the RAAS by competing with aldosterone at the level of the mineralcorticoid receptors.[20] Although natural micronized progesterone is available and effective for HT, most commercial combinations contain a synthetic progestogen derived from 19-nortestosterone (ie, norethisterone acetate) or 17-α-hydroxyprogesterone (ie, medroxyprogesterone acetate). All the progestogens/progestins, currently used in HT preparations, exert a progestogenic activity to contrast the proliferative effects of estrogen on the uterine endometrium; however, none of them has an antimineralcorticoid activity. Drospirenone (DRSP) is a novel progestin derived from 17-α-spironolactone, with antialdosterone and antiandrogenic effects.[21] The combination DRSP/estradiol (E_2) is approved for the treatment of estrogen deficiency symptoms in postmenopausal women. The compound, alone or in combination with analapril[22] or hydrochlorothiazide,[23] showed significant antihypertensive effects in postmenopausal hypertensive women. Furthermore, DRSP/E_2 seems to have significant antihypertensive effects in patients with and without type 2 diabetes who concomitantly make use of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.[24]

The aim of the present study was to compare, in healthy normotensive postmenopausal women, the effects of DRSP/E_2 and norethisterone acetate/E_2 on 24-hour ambulatory blood pressure and other surrogate markers (reduced brachial artery flow-mediated vasodilatation, Doppler evaluation of ophthalmic artery) of cerebrovascular and cardiovascular risk.

METHODS

Participants

Thirty white (native Italians) postmenopausal women (follicle-stimulating hormone >40 IU/L, E_2 <100 pmol/L) attending the Menopause Outpatient Clinic of Bologna University participated in the study. The participants were selected among those who, during the screening evaluation, had undergone a natural menopause at least 12 months before the study, had an ultrasonographic thickness of the endometrial stripe less than 4 mm, and had a negative Papanicolaou smear and mammography. Furthermore, the participants who entered the study presented with a systolic blood pressure (SBP) of 120 mm Hg or less and a diastolic blood pressure (DBP) of 80 mm Hg or less. The blood pressure was taken with the cuff technique using a mercury sphygmomanometer applied to the nondominant arm.[25] The diastolic reading was taken when the sounds disappear (Korotkoff phase V).[25] The measurement was repeated after 10 minutes, and the arithmetic mean of the two measurements was used.

None of the women had received HT or other hormonal treatments for at least 6 months before the study.

Participants who underwent bilateral oophorectomy, and women affected by obesity (body mass index [BMI] > 30 kg/m^2), diabetes, hypertension (SBP >140 mm Hg or DBP >90 mm Hg), cardiovascular, or cerebrovascular or renal disease or those with gynecological problems (uterine and/or adnexal masses) were excluded from the study. Similarly, heavy smokers (>10 cigarettes/d) were not included.

The study protocol was in accordance with the Helsinki II declaration and was approved by the Hospital Research Review Committee. The study was conducted between January 2006 and December 2007 in the Department of Obstetrics and Gynecology of the Bologna University School of Medicine. Women participated in the study after an informed written consent was obtained.

Study design

After the first screening evaluation, participants were subsequently assessed with a detailed history and medical examination, and fasting blood samples were drawn for testing plasma concentrations of nitrites (NO_2^-)/nitrates (NO_3^-). Participants were further submitted to utero-ovarian ultrasonographic analysis and to color Doppler evaluation of ophthalmic arteries. In addition, ultrasonographic and color Doppler analysis of brachial artery flow-mediated vasodilatation and 24-hour ambulatory blood pressure monitoring were performed.

Participants were randomly submitted to oral daily treatment with Angeliq (drospirenone 2 mg + E_2 1 mg; Bayer-Schering Italia, Milan, Italy) (group 1; n = 15) or continuous oral administration of Activelle (norethisterone acetate 0.5 mg + E_2 1 mg; Novo Nordisk Farmaceutici, Roma, Italy) (group 2; n = 15). Randomization was performed by opening sequentially numbered sealed envelops containing treatment allocation determined by a random number table. The two treatments were allocated in a 1:1 ratio.

The duration of the study was 6 months, and the participants were studied in basal condition and after 6 months of the therapy.

Ultrasound and color Doppler examination

All participants underwent ultrasonographic evaluation of the pelvic organs and the endometrial thickness by using a multifrequency vaginal transducer (Voluson 730 Expert Sonography System; GE Healthcare Ultrasound; Medex, Padua; Italy). To obtain standardized conditions, all participants were studied between 8:00 and 11:00 AM. They voided their bladders and rested for at least 10 minutes before being scanned in a noiseless laboratory with constant heat and light. For endometrial evaluation, multiple sagittal and transverse planes through the uterine fundus and lower segments were examined. Measurements were taken from a sagittal sonogram through the thickest area of endometrium from the outermost border on one side to that on the other. Immediately after the ultrasonographic (US) evaluation, a color Doppler analysis of ophthalmic arteries was performed using a multifrequency linear array (Voluson 730 Expert color Doppler). A 50-Hz filter was used to eliminate low-frequency signals originating from vessel wall movements. The maximal Doppler ultrasonography energy was less than 80 mW/cm^2.

This intensity is within the safety limits suggested by the American Institute for Ultrasound in Medicine. Briefly, the transducer was bilaterally placed on the closed eyelid after coupling gel was applied. To prevent artifacts, care was taken to avoid excessive pressure on the globe. Horizontal scans through the eye and the orbit were then performed. The sample volume was oriented superiorly and medially to the optic nerve, lateral to the visible hypoechogenic line representing the optic nerve.[26] The mean duration of ophthalmic artery scan was never more than 1 minute per eye. The angle of insonation was always adjusted to obtain maximal color intensity. When good signals were obtained, blood flow velocity waveforms were recorded by placing the sample volume across the vessel and activating the pulsed Doppler mode. The pulsatility index (PI), defined as the difference between the peak systolic and end-diastolic flow divided by the mean maximal flow velocity, was electronically calculated by the machine. The PI has been shown to reflect blood flow impedance and may be used when the end-diastolic frequency shift is absent or reversed. For each examination, the mean value of three consecutive waveforms was obtained. No significant differences between the PIs of the left and right side of the ophthalmic arteries were observed, and therefore, the average value of both side arteries was used. The correlation between PIs and heart rate was not tested. In view of the difficulty in interpreting the PI in low-impedance vascular beds such as the cerebral circulation (ophthalmic artery), the downstream "back pressure" (BP) was calculated using the model proposed by Gosling et al.[27] According to this model, BP is the sum of the arteriolar vasomotor tone and intracranial pressure and can be estimated using PI, SBP, and DBP: $BP = DBP + (SBP - DBP) \times (1/3 - 1/PI)$.[27] An indication of the within-participant precision of the BP was obtained by analyzing, in 10 participants, the recorded parameters, at a single setting, on three occasions at 2-minute intervals. An analysis of variance of the results gave a mean coefficient of variation of 6.3%, which was not significantly different from replicate measurements.

Ultrasound and color Doppler analyses were performed by a single examiner (C.B.) who was unaware of the participant's HT treatment.

Brachial artery flow-mediated vasodilatation

Immediately after the above-described US and Doppler scanning, a high-resolution ultrasound transducer was placed over the brachial artery to measure its diameter before and after reactive hyperemia.[28,29] Briefly, the right brachial artery was evaluated with continuous scanning held for 30 seconds (by using a multifrequency linear array transducer—Voluson 730 Expert) over a longitudinal section 5 to 7 cm above the right elbow. The skin was marked to ensure the same transducer position throughout the examinations. A blood pressure cuff around the upper arm was then inflated to a pressure of 200 mm Hg for 5 minutes. This caused ischemia and consequent dilatation of downstream resistance vessels. The subsequent cuff deflation induced a brief high-flow condition through the brachial artery (reactive hyperemia) due to the intense nitric oxide release from the endothelial cells. After this, a second scan was performed and the brachial artery was analyzed at 15, 60, and 120 seconds. The ultrasound images were recorded and subsequently analyzed off-line. The diameter of the brachial artery was measured from the tunica intima at a fixed distance from the chosen marker. Flow-mediated vasodilatation was also determined as the percent change from baseline to 15 and 120 seconds after sudden deflation subsequently to arm ischemia. A Doppler analysis of brachial artery (Voluson 730 Expert color Doppler) was performed, and the PIs were registered (as absolute values and percent variations) at baseline and just after US measurements of brachial artery. Brachial artery flow-mediated vasodilatation was evaluated by a single examiner (C.B.) who was unaware of the participant's HT treatment.

24-Hour blood pressure monitoring

Ambulatory blood pressure monitoring was performed using a portable lightweight device (SpaceLab 90121; Critikon, Goldendale, WA) applied to the nondominant arm.[30,31] The accuracy of the ambulatory blood pressure monitoring was confirmed in each participant by two simultaneous auscultations and sphygmomanometry. Systolic and diastolic blood pressure readings differed by less than 5 mm Hg. Participants wore the device for 24 hours, with measurements being taken every 30 minutes during the day (8:00 AM-10:00 PM) and hourly overnight (10:00 PM-8:00 AM). Participants were asked to sleep between 10:00 PM and 8:00 AM and to maintain their usual daily activities. Participants received verbal and written instructions on the use of the devices and completed a diary to record posture, meals, diurnal activities, and sleep. The 24-hour blood pressure monitoring was considered statistically acceptable in the presence of more than 75% successful measurements. Different 24-hour, daytime and nighttime, and wake-up variables were calculated: SBP, DBP, mean arterial pressure (= [SBP + (2/3 DBP)/3]). Normal blood pressure values were considered less than 135/85 mm Hg for daytime, less than 120/75 mm Hg for nighttime, and less than 130/80 mm Hg for 24 hours. The percentage of recordings exceeding these reference values was calculated. The 24-hour heart rate was recorded. The results were separately analyzed by two researchers (N.P. and A.C.).

Assays

Peripheral blood flow was obtained from all participants between 8:00 and 11:00 AM, after an overnight fast, on the same day that US and Doppler examinations took place. An aliquot of peripheral blood was immediately centrifuged and serum stored at −70° until assays. Nitric oxide (NO) production was assessed by monitoring serum levels of stable oxidation products of NO metabolism (NO_2^-/NO_3^-). Because very little or no NO_2^- is normally found in the serum, we did not attempt to differentiate between NO_2^- and NO_3^- amounts; therefore, we report our results as NO_2^-/NO_3^-. The NO_2^-/NO_3^- were assayed at Modena-Reggio

Emilia University (F.F.) with the Greiss reaction with procedures previously described.[32,33] It involves a diazotization of endogenous nitrites with sulfanilamide followed by a coupling with *N*-(1-naphtyl)ethylene-diamine. The absorbance of samples was read at 548 nm by using a spectrophotometer. The serum NO_2^-/NO_3^- values were expressed in micromoles per liter. A useful standard curve ranged from 2.5 to 80 μmol/L. The intra-assay coefficient of variance was 4.0%. During the 6-month period of the study, the interassay coefficient of variance was 8.1%.

Statistical Analysis

Sample size calculations, assuming 80% power to detect 5 μmol/L changes in circulating NO_2^-/NO_3^- levels between groups, indicated the need of 12 participants in each group. Statistical analysis (SPSS version 11.5; SPSS Inc, Chicago, IL) was performed using the one-way analysis of variance test. For repeated measures, we used the Wilcoxon test. The relationship between the parameters analyzed was assessed using the stepwise linear regression method. A *P* value of 0.05 was considered statistically significant. Data are presented as mean ± SD, unless otherwise indicated. The statistical analysis was performed by a single researcher (P.B.).

RESULTS

All 30 women completed the study. Groups 1 and 2 did not differ in age (52.6 ± 3.1 y vs 51.7 ± 2.8 y; range, 48-56 y) or in BMI (24.2 ± 2.1 kg/m^2 vs 24.7 ± 1.8 kg/m^2; range, 21-27 kg/m^2). After the 6-month therapy, the BMI had remained stable in both group 1 (24.0 ± 1.9 kg/m^2) and group 2 (24.7 ± 1.7 kg/m^2). The mean time since menopause was 2.1 ± 1.1 years (range, 1-4 y).

In all the participants, HT relieved the vasomotor symptoms within the first month of treatment. During the therapy, no important adverse effects were registered. Two women in group 1 and two women in group 2 showed a moderate spotting in the first 3 months of the therapy. In two women in group 2 and in one woman in group 1, a temporary and weak bloating sensation with water retention and mammary tenderness was registered.

The US assessment allowed the measurement of the endometrial thickness in 100% of the women. The measurement was always less than 4 mm, and no significant differences were registered among the groups either before or after the 6 months of treatment. Within 3 months of treatment, all participants showed inactive/atrophic endometrium.

At the Doppler analysis, the basal PI of the ophthalmic artery (1.56 ± 0.22 vs 1.58 ± 0.16) was similar in groups 1 and 2. The basal ophthalmic artery BP (group 1: 54.4 ± 6.5 mm Hg; group 2: 51.1 ± 5.1 mm Hg) did not differ among the studied participants. After 6 months, the ophthalmic artery PI did not change either in group 1 (1.52 ± 0.20) or in group 2 (1.50 ± 0.24). No differences were found between the groups. The ophthalmic artery BP (group 1: 49.2 ± 3.8 mm Hg; group 2: 50.6 ± 4.1 mm Hg) did not change after the 6 months of therapy.

The circulating NO_2^-/ NO_3^- values were not different between groups 1 and 2 either in basal conditions (26.3 ± 6.5 μmol/L vs 23.0 ± 7.2 μmol/L) or after therapy (28.8 ± 5.9 μmol/L vs 25.5 ± 4.7 μmol/L).

In basal conditions and after the 6-month therapy, the brachial artery diameter, at baseline, was similar in all participants (Fig. 1). After the reactive hyperemia, a similar vasodilatation was observed in all the women, and the persistence of the effect was not significantly different between groups 1 and 2 (Fig. 1). The percent change at 15 and 120 seconds was superimposable in the two groups (Fig. 1). The PI of the brachial artery did not show any difference in groups 1 and 2 either in basal conditions or after therapy (Fig. 2). The percent change at 15 and at 120 seconds was similar in the two groups (Fig. 2).

The 24-hour blood pressure monitoring in the two groups showed no significant differences in the 24-hour, daytime, and nighttime values in basal conditions and after the therapy (Table 1). The percentages of values greater than 135 mm Hg in the SBP and greater than 85 mm Hg in the DBP during daytime and the percentages of values greater than 120 mm Hg in the SBP and greater than 75 mm Hg in the DBP during sleep time were similar in all the participants both before

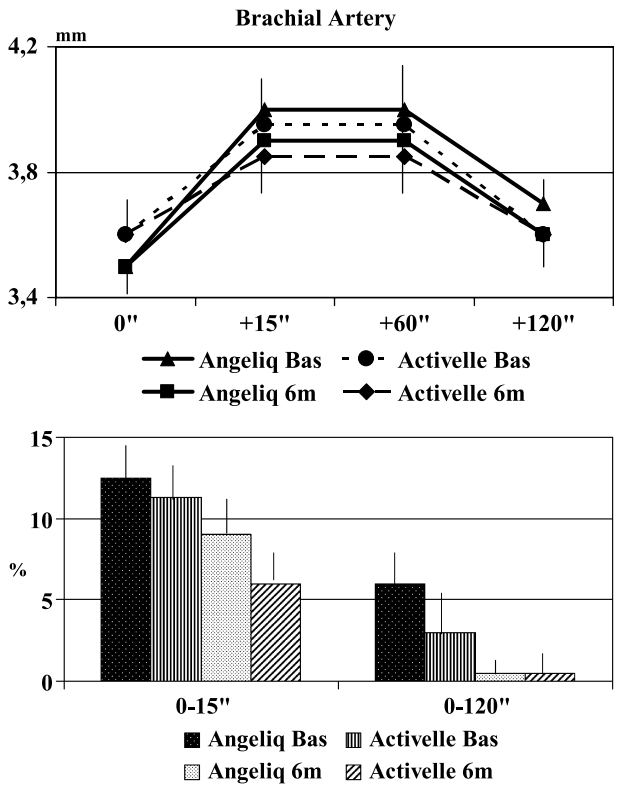

FIG. 1. Postischemic flow-mediated dilatation of brachial arteries in Angeliq and Activelle postmenopausal treated women. The brachial artery diameter (mm) was evaluated at baseline and after 6 months of treatment. **Upper panel**: at time 0 second and after the reactive hyperemia (time 15-120), the brachial artery diameter (mm) was similar in the two groups both at baseline and after 6 months of treatment. **Lower panel**: the percentage change at 15 and 120 seconds after the reactive hyperemia showed no difference between the two groups both at baseline and after 6 months. Bas, baseline.

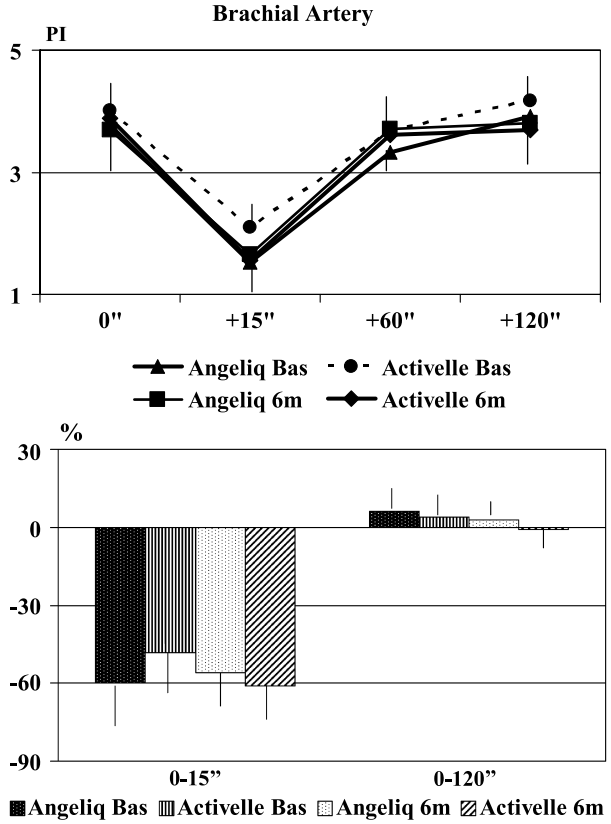

FIG. 2. Postischemic flow-mediated dilatation of brachial arteries in Angeliq and Activelle postmenopausal treated women. The brachial artery pulsatility index (PI) was evaluated at baseline and after 6 months of treatment. **Upper panel**: at time 0 second and after the reactive hyperemia (time 15-120), the brachial artery PI was similar in the two groups both at baseline and after 6 months of treatment. **Lower panel**: the percentage change at 15 and 120 seconds after the reactive hyperemia showed no difference between the two groups both at baseline and after 6 months. Bas, baseline.

and after therapy (Table 1). All participants were found to be dippers normally (nocturnal reduction ≥10% in comparison with diurnal values). The wake-up blood pressure values before and after the treatment were similar in the studied participants (Table 1). The 24-hour heart rate is reported in Table 1. No significant relationship was seen between the different parameters.

DISCUSSION

The decrease in the levels of endogenous female sex hormones during menopause causes unpleasant physical and psychological symptoms of the climacteric syndrome. Vasomotor symptoms and urogenital atrophy may be significantly improved by estrogen therapy. However, in women with an intact uterus, the estrogen-only therapy can cause endometrial hyperplasia and increase the risk of endometrial carcinoma. Therefore, to counteract the proliferative effects of estrogen on the uterine endometrium, progestogens are currently used in HT preparations. Recently, large randomized prospective studies underlined that the risk of hypertension and the risk of cardiovascular and cerebrovascular pathologies are increased in current estrogen/progestogen users. Because drospirenone potentially lowers blood pressure without opposing the positive effects of estrogens on circulating lipids, it was postulated that combined with E_2, it may be the ideal progestogen in HT.[21]

In the present study, we compared, in nonobese and relatively young women, the effects of two different HT formulations containing drospirenone and norethisterone acetate. Both therapies were similarly effective in improving vasomotor symptoms rapidly and in showing a protective effect on the endometrium and did not cause an increase in body weight or any other important adverse effects. In addition, in women without any other apparent disease, the two therapies seemed not to alter the surrogate markers of cardiovascular and cerebrovascular risk.

The vascular endothelium is a complex organ with a multitude of autocrine, paracrine, and endocrine properties.[34] Endothelial dysfunction in peripheral arteries correlates with the presence of coronary artery endothelial dysfunction and angiographically proven coronary artery disease.[35] Furthermore,

TABLE 1. *24-Hour blood pressure monitoring in postmenopausal women treated with Angeliq or Activelle*

	Group 1 (n = 15)		Group 2 (n = 15)		
	Basal	6 mo	Basal	6 mo	Significance
24-h SBP, mm Hg	118 ± 6	116 ± 3	112 ± 3	115 ± 2	NS
24-h DBP, mm Hg	70 ± 9	69 ± 6	68 ± 2	68 ± 4	NS
24-h MAP, mm Hg	89 ± 7	86 ± 8	82 ± 2	84 ± 4	NS
0800- to 2200-h SBP, mm Hg	118 ± 14	119 ± 8	114 ± 9	116 ± 8	NS
0800- to 2200-h DBP, mm Hg	79 ± 12	77 ± 6	70 ± 3	72 ± 5	NS
0800- to 2200-h MAP, mm Hg	86 ± 13	85 ± 9	84 ± 2	82 ± 3	NS
0800- to 2200-h % SBP > 135 mm Hg	2.7 ± 1.3	0	1.9 ± 0.5	0	NS
0800- to 2200-h % DBP > 85 mm Hg	1.9 ± 1.5	0	0	0	NS
2200- to 0800-h SBP, mm Hg	117 ± 11	114 ± 7	109 ± 7	111 ± 8	NS
2200- to 0800-h DBP, mm Hg	76 ± 12	74 ± 5	65 ± 6	68 ± 7	NS
2200- to 0800-h MAP, mm Hg	90 ± 3	86 ± 7	79 ± 5	78 ± 9	NS
2200- to 0800-h % SBP >120 mm Hg	3.5 ± 1.0	0	3.5 ± 2.5	0	NS
2200- to 0800-h % DBP >75 mm Hg	2.1 ± 2.1	1.3 ± 2.1	2.5 ± 1.3	0	NS
Wake-up SBP, mm Hg	113 ± 12	116 ± 4	102 ± 3	108 ± 9	NS
Wake-up DBP, mm Hg	64 ± 9	67 ± 7	61 ± 13	63 ± 7	NS
Heart rate	63 ± 7	66 ± 7	64 ± 9	61 ± 4	NS

DBP, diastolic blood pressure; MAP, mean arterial pressure; NS, not significant; SBP; systolic blood pressure.

even in the absence of any clinical sign of coronary artery disease, the patients with peripheral endothelial dysfunction seem to be at increased risk for future myocardial infarction, coronary revascularization, and cardiac death. In addition, endothelial dysfunction precedes overt vascular disease by years. Despite the fact that no gold standard exists for the evaluation of endothelial function, the measurement of the flow-mediated dilatation in the brachial artery (a well-tolerated and noninvasive procedure) is the most studied and promising method for clinical application. Anderson and Mark[36] in 1989 first demonstrated that blood flow through the brachial artery is increased in response to transient vascular occlusion. They showed that healthy arteries present an increase in diameter in the range of 5% to 15%, whereas brachial artery flow increases five-to sixfold. In our study, conducted in very standardized and easily reproducible conditions, all participants showed a basal normal flow-mediated dilatation in the brachial artery (intense postischemic vasodilatation and maintenance of reactive hyperemia after 120 s). A 6-month therapy with drospirenone or norethisterone acetate did not modify the normal flow-mediated dilatation in the brachial artery. No different results were observed in performing Doppler analysis of brachial artery PIs. The $(NO_2^-)/(NO_3^-)$ plasma levels were stable both before and after the treatments and showed similar circulating values in all the studied participants. Thus, we determined that in healthy normotensive women, HT does not alter NO release/production, does not increase the NO degradation, and does not impair the endothelium-dependent vasodilatation.

Whether HT may be associated with hypertension is controversial. In some susceptible women estrogens could increase blood pressure via the RAAS.[20] Renin is a hormone (produced in the kidney) that converts angiotensinogen to angiotensin I, which, in turn, is transformed to angiotensin II by angiotensin-converting enzyme. Angiotensin II stimulates aldosterone secretion (from the adrenals) with consequent sodium retention and potassium excretion. Angiotensin II is also a potent vasoconstrictor and raises blood pressure. Drospirenone has been reported as a safe option for women using HT.[21] Its antimineralcorticoid and antialdosterone effects seem to decrease water retention and blood pressure. In fact, the drospirenone/E_2 combination, compared with placebo, was associated with slight but significant reductions in SBP and DBP.[22-24] In our study, using 24-hour ambulatory monitoring, we did not demonstrate, before and after 6 months of therapy, any difference between dropirenone and norethisterone regimens in the total 24-hour, daytime, or nighttime blood pressure. No differences were found in 24-hour heart rate (a precocious indicator of increased left ventricular mass in women with newly diagnosed, untreated hypertension).[37] In the normotensive and hypertensive populations, the nocturnal dipping and the wake-up surge are prognostic indicators of target organ damage and of cardiovascular morbidity and mortality. In our two groups of participants, the nocturnal dipping and the wake-up surge did not differ significantly either before or after therapy.[38-40] Similarly, the percentages of values greater than 135 mm Hg in the SBP and greater than 85 mm Hg in DBP during the day time and the percentages of values greater than 120 mm Hg in the SBP and greater than 75 mm Hg in DBP during the sleep time were similar in all the participants both before and after therapy regardless of the HT they used. Although we are aware that in the present pilot study, the number of participants is limited and the duration of the observational period is short, we believe that in normotensive postmenopausal participants, a 6-month HT treatment, independently of the progestogen used, is not enough to allow the estrogen activation of the RAAS. Alternatively, we may speculate that in healthy women, estrogens interfere only slightly with the RAAS and that the homeostatic processes may compensate for the induced modifications. Oelkers[20,41] recently reported in healthy women that the induced rise in angiotensin II levels caused by estrogen reduces the level of renin secretion in the kidney by a negative feedback process, so that only small and not clinically significant increases in angiotensin II and aldosterone occur. Obviously, we cannot exclude the possibility that a more prolonged exposure to estradiol may lead to an incomplete compensatory renal fall in renin secretion and to a consequent increase of plasma renin, angiotensin II, and aldosterone concentrations.

In the present study, we also analyzed, in the basal condition and after 6 months of Angeliq or Activelle treatment, the hemodynamic properties of ophthalmic arteries. The ophthalmic artery is a small vessel arising from the internal carotid artery. It has a variable course and branching pattern. Cerebral vessels are morphologically and physiologically similar to the arteries of the eye. Thus, knowledge of vascular changes in the ophthalmic arteries may be useful in assessing changes in global cerebral perfusion. Powers et al[42] showed that decreased/reversed ophthalmic artery flow is often associated with diminished cerebral perfusion and is indicative of inadequate collateral circulation via the Circle of Willis. Furthermore, recently, Ikram et al[43] observed that retinal arteriolar narrowing may precede the development of systemic hypertension. Our study confirmed that the Doppler examination of the ophthalmic artery is an easily performed technique (<1 min/eye)[26] and showed similar ophthalmic artery PI values in drospirenone- and norethisterone acetate–treated participants. The ophthalmic artery BP[27] (the sum of arteriolar vasomotor tone and intracranial pressure) did not show any significant difference among the groups. The above data underline that normotensive, healthy women treated with 6 months of HT do not show any worsening of the cerebral vascularization.

CONCLUSIONS

A 6-month HT with drospirenone/E_2 or norethisterone acetate/E_2 is equally effective in inducing a rapid improvement of vasomotor symptoms and a protective effect on the endometrium and causes no increases in body weight or other significant adverse effects. In addition, in women without any

other apparent disease, the two therapies seem to not alter the surrogate markers of cardiovascular and cerebrovascular risk.

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