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A Randomized Controlled Trial of Low Dose Hormone Therapy on Myocardial Ischemia in Postmenopausal Women with No Obstructive Coronary Artery Disease: Results from the National Institutes of Health – National Heart, Lung, and Blood Institute (NHLBI) – Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Abstract

Background—Compared with men, women have more evidence of myocardial ischemia with no obstructive CAD. While low endogenous estrogen levels are associated with endothelial dysfunction, the role of low dose hormone therapy has not been fully evaluated. We postulate a 12-week duration of low dose hormone replacement therapy is associated with myocardial ischemia and endothelial dysfunction.

Methods and Results—Using a multicenter, randomized, placebo-controlled design, subjects were randomized to receive either 1 mg norethindrone/10 mcg ethinyl estradiol (1/10 NA/EE) or placebo for twelve weeks. Chest pain and menopausal symptoms, cardiac magnetic resonance spectroscopy (MRS), brachial artery reactivity (BART), exercise stress testing, psychosocial

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questionnaires were evaluated at baseline and exit. Recruitment was closed prematurely due to failure to recruit following publication of the Women's Health Initiative hormone trial. Of the 35 women who completed the study, there was less frequent chest pain in the treatment group compared to the placebo group (p=0.02) at exit. Women taking 1/10 NA/EE also had significantly fewer hot flashes/night sweats (p=0.003), less avoidance of intimacy (p=0.05), and borderline differences in sexual desire and vaginal dryness (p=0.06). There were no differences in MRS, BART, compliance or reported adverse events between the groups.

Conclusions—These data suggest that low dose hormone therapy improved chest pain symptoms, menopausal symptoms and quality of life, but did not improve ischemia or endothelial dysfunction. Given that it was not possible to enroll the pre-specified sample size, these results should not be considered definitive.

Compared to men, women have more evidence of myocardial ischemia in the setting of no obstructive coronary artery disease (CAD)[1]. Coronary endothelial dysfunction has been suggested as a mechanism that may contribute to signs and symptoms of ischemia in the absence of severe coronary obstruction2. Preliminary evidence suggests that low estrogen levels may contribute to endothelial dysfunction3–4, and that estrogen replacement abolishes this effect[3,5–6]. But this has not been evaluated in women with symptoms and signs of myocardial ischemia in the absence of severe obstructive CAD.

The goal of this Women's Ischemia Syndrome Evaluation (WISE) ancillary study was to evaluate the effect of low dose hormone replacement therapy with 1 mg norethindrone/10 mcg ethinyl estradiol (1/10 NA/EE) in postmenopausal women with a history of chest discomfort, myocardial ischemia and no obstructive CAD on: 1) inducible myocardial ischemia measured by MRS, 2) endothelial dysfunction assessed by BART, 3) physical functional disability assessed by exercise testing, and 4) quality of life assessed by cardiac symptoms and psychological questionnaires.

METHODS

The WISE is a National Heart, Lung and Blood Institute (NHLBI) sponsored study to improve the diagnostic evaluation of ischemic heart disease in women. Institutional Review Boards at each site approved the overall protocol as well as this ancillary study protocol, which is in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Data were monitored by an independent Data and Safety Monitoring Committee. Details of the WISE protocol and design are previously published[7]. A subgroup of women from the Universities of Florida and Alabama sites was screened for this ancillary study with informed consent to participate in the additional testing, treatment and follow-up detailed below.

The ancillary study was a randomized, placebo-controlled, double-blind design among women and has been registered at ClinicalTrials.gov with an identifier number NCT00600106. The inclusion criteria included being postmenopausal by WISE criteria7, no use of hormone therapy in the last 6 weeks, with a history of chest discomfort and normal or only minimally diseased (<50% diameter stenosis) epicardial coronary arteries measured by the WISE Angiographic Core Laboratory[8], and evidence of myocardial ischemia. Myocardial ischemia was defined for this trial as an abnormal result on any of the following qualifying tests: 1) abnormal P-31 gated MRS characterized by a fall in quantitative PCr/ATP ratio >20% from rest during handgrip exercise; 2) positive treadmill exercise stress test (>1.0 mm horizontal/ downsloping or >1.5 upsloping ST segment depression measured 0.08 msec after the J point); 3) reversible stress radionuclide perfusion defect > equivocal and not attributable to breast/imaging artifact; 4) coronary flow reserve <2.25 to intracoronary

adenosine. Exclusion criteria included inability to withdraw vasoactive medication, contraindication to hormone therapy, or comorbid illness that precluded participation.

Subjects were randomized to receive either 1 mg norethindrone/10 mcg ethinyl estradiol (1/10 NA/EE) or placebo for twelve weeks, as well as to discontinue their vasoactive medications, except beta-blockers and sublingual nitrates, for at least 12 hours prior their baseline evaluation. Baseline assessments using previously published WISE methods including MRS, BART, exercise stress testing and coronary flow reserve, as well as WISE psychosocial questionnaire, SF-36, and blood lipid and hormone level. Because the MRS data were acquired using different instruments and techniques at the sites (Phillips MR and DRESS technique at University of Alabama, and GE MR and ISIS technique at University of Florida, respectively), spectra were read by site investigators blinded to subjects' clinical information and treatment assignment. WISE blood lipid and hormone core laboratories used previously published methods9–10. Psychosocial and Quality of Life (QOL) questionnaires included Cook Medley Hostility Scores (CMH)11, Beck Depression Inventory (BDI)12, Autonomic Perception Questionnaire (APQ)13, SF-3614–15, and the Menopause-specific quality of life questionnaire that focuses on hot flashes, poor memory, change in sexual desire, vaginal dryness and avoiding intimacy16. Patients were contacted by telephone at 2, 6, and 10 weeks to enhance study compliance and assess status. At the exit visit following 12 weeks of drug treatment, all tests were repeated.

Statistical Analysis

Sample Size Considerations—The recruitment goal for this trial was 74 women, 37 assigned to each of two groups: placebo and 1/10 NA/EE. The sample size calculation was based on the primary measures of interest: 1) % change of PCr/ATP in myocardium by MRS at stress testing compared to at rest; 2) % change in ratio of brachial artery diameter at peak hyperemia after release of occlusion compared to before occlusion. Both measures were expressed as percent change and as continuous variables and standard deviations (SDs). With 74 participants the differences between the 1/10 NA/EE and placebo groups that can be detected as statistically significant for a two-sided test (α=0.05 and β=20%) are as follows: 7.5% (SD 10.9%) change in PCr/ATP and a 7.1% (SD 10.3%) change in brachial artery diameter.

Data analysis—Data were presented in tables as means and SDs for continuous variables and frequencies for categorical variables. Comparisons between the placebo and 1/10 NA/EE groups were done using Wilcoxon rank sum test for continuous measurement and Fisher's Exact test for discrete data. The strategy of analysis was 'intention to treat' with comparing the study groups in term of the treatment to which they were randomly allocated. All tests were two-sided with p values <0.05.

RESULTS

A total of 1142 women were screened by chart review for possible entrance and most were not eligible due to obstructive coronary artery disease observed during coronary angiography. Of the 57 eligible women who entered the testing phase, 37 women went on to randomization. There was no difference in the type of qualifying test by treatment group (p=0.87). Among the 37 women, 30 (81%) had previously used hormone therapy, with a mean prior use of 10.7±9.5 years, and 14 (38%) had used hormone therapy in the prior 3 months and washed out to participate. There were no differences in prior or current hormone therapy use between two groups.

Baseline characteristics

Two groups were comparable in baseline characteristics, except more women in placebo group has a history of hypertension, higher heart rate (Table 1), and higher frequency of using antihypertensive angiotensin converting enzyme (ACE) inhibitors (47% vs. 11%, p=0.03) compared to 1/10 NA/EE group. At study exit, characteristics and medication use remained consistent with baseline findings, although medication dose changes were not collected. There were no differences in comparing two groups regarding chest pain frequency, CMH, BDI, or APQ results, as well as BART, exercise, or MRS (Table 2), menopause symptom, or SF-36 scales (Table 3). In exercise stressing testing, however, there is a trend in improved ST segment depression in 1/10 NA/EE group compared with placebo group (0.21±0.19 vs. −0.35±0.22, p=0.07).

Response to Intervention –Exercise Stress Testing, Endothelial Function, and Myocardial Ischemia

Notably, 7/35 (20%) of the women could not perform the exercise stress test within the time frame at the exit visit due to orthopedic injury or surgery. Among those women able to exercise, there were trends toward improvements among the 1/10 NA/EE group in functional capacity, which was measured as metabolic equivalents (METs), exercise duration and exercise-induced chest pain that did not reach statistical significance (Table 2). There was no difference for the BART (Table 3). Among the 35 women, 28 baseline and 26 exit MRS results were technically adequate for spectral analyses with rest, handgrip exercise and recovery spectra. There was no difference in the cardiac MRS between groups (Figure 1), with both groups demonstrating similar trends toward improvement with repeat testing. Further analyses with regard to hypertension, baseline use of ACE-inhibitors, or change in use of ACE-inhibitors did not alter these cardiac MRS or BART results.

Response to Intervention – Chest Pain, Menopausal Symptoms and Quality of Life

While there is no difference in chest pain frequency at baseline, at study exit women in the 1/10 NA/EE group reported less frequent chest pain than those in the placebo group (p=0.02)(Figure 2). While both groups reported a high frequency of hot flashes/night sweats, poor memory, and vaginal dryness at baseline, at the exit, women assigned 1/10 NA/EE reported significantly fewer hot flashes/night sweats (p=0.003), less avoidance of intimacy (p=0.05), and trends were observed (p=0.06) for less change in sexual desire and vaginal dryness (Table 2) compared with those assigned placebo.

There was no difference in the CMH questionnaire, BDI or APQ results for either group (data not shown). Women in the 1/10 NA/EE group had higher scores in the physical role function in SF-36 than those in the placebo group (p=0.01), indicating better functioning at work and other daily activities with less limitation in performing in activities (Table 2).

Study Recruitment, Compliance and Adverse Events

In the year following publication of the Women's Health Initiative (WHI) hormone trial results[17], women eligible for participation regularly declined enrollment so recruitment was closed prior to reaching the planned sample size. Of the 37 women randomly assigned to treatment, 35 completed the study and 2 withdrew. One woman withdrew due to time constraints, and the other woman withdrew following the publication of the WHI findings.

There were no differences in study medication compliance assessment, in which excellent compliance was defined as >85% by pill count, by randomization group (100% and 78% in placebo and 1/10 NA/EE groups, respectively, p=0.23). One woman in the 1/10 NA/EE group had a hospitalization for angina and a stroke, and one woman in the 1/10 NA/EE was hospitalized for biliary colic (p=0.23).

DISCUSSION

These results suggest that while low dose hormone therapy reduces chest pain, menopausal symptoms and improves quality of life in symptomatic women with evidence of myocardial ischemia but no obstructive CAD, there was no significant improvement in the variables assessing endothelial dysfunction, exercise testing and ischemia measured by cardiac MRS. These results suggest that hormone therapy may be helpful in postmenopausal women with myocardial ischemia and no obstructive CAD for symptom management, however 12-week treatment period does not appear to have a prominent effect on either measures of myocardial ischemia or endothelial dysfunction. Given that it was not possible to enroll the pre-specified sample size, the results should be interpreted with caution.

Our findings are consistent with prior reports. Prior WISE study findings indicate that a history of hormone therapy was linked with less menopausal symptoms and better QOL in symptomatic women with or without obstructive CAD[18]. These findings confirm and extend prior published trial reports in women with chest pain, abnormal stress testing and no obstructive CAD[19]. Previous study has suggested that estrogen hormone therapy is associated with improved exercise-induced angina and exercise capacity[20]. While our data suggest a trend for improved exercise stress testing parameters at exit for 1/10 NA/EE group, the absence of statistical significance may be due to low statistical power, precluding a definitive result. Given the current data trend, a total of 100 women would have been required to detect the observed exit differences in ST segment depression and chest pain occurrence. Our current study findings extend prior findings to include improvement in daily life angina. Notably, others have suggested that while estrogen-testosterone hormone therapy was associated with improved emotional well-being in postmenopausal women with angina and “normal” angiograms[21], it was not associated with less chest pain occurrence and/or its threshold during exercise[22]. Comparing their data with ours suggests that estrogen without testosterone may be more beneficial for chest pain and related symptoms.

Prior reports evaluating coronary endothelial function using high pharmacological doses of estrogen acutely suggested improvement[3]. But subsequent reports evaluating chronic and more physiological hormone therapy and peripherally measured endothelial function have mixed results with regard to a beneficial effect[23–25]. Additionally, a number of hormone therapy trials now consistently document a risk of increased cardiovascular disease events in postmenopausal women[17, 26–28], indicating that any apparent beneficial effect on indices of endothelial function may be outweighed by adverse vascular effects leading to clinical outcomes. The relevance of this to our cohort is unclear, because women in our and prior cohorts[2] are substantially younger than most of these prior hormone trials. More recent studies suggest a lower incidence of cardiovascular events among women who initiated hormone therapy at younger age[29–30]. A study of myocardial blood flow has suggested that hormone therapy may normalize flow only among women without risk factors[31], although prospective testing is needed. While the one cardiovascular adverse event experienced in the current study was in a woman randomized to the hormone therapy, we were clearly underpowered and exposure was too brief to evaluate clinical events in present study.

No prior studies have employed cardiac MRS to assess high energy phosphate metabolism and this is considered as a biochemical reference for myocardial ischemia. We have previously demonstrated that patient with myocardial ischemia measured by cardiac MRS has a higher risk for adverse cardiovascular events, including death, myocardial infarction, and stroke, re-hospitalization and repeat coronary angiography[32]. However, our cardiac MRS results showed a relatively wide variability in PCr/ATP change with isometric handgrip stress at baseline. Compared with our findings in two other subgroups[32–33] reported from the WISE, the SD was approximately 2 fold greater in this ancillary study,

suggesting that our limited sample size again may have precluded our ability to detect an effect of the intervention. The trend toward improvement in both groups is suggestive of a training effect; however these results could be due to changes in other anti-ischemia therapy dosing, spontaneous biological and measurement variability, or the measurement phenomenon of regression to the mean. Exploration of this finding in relation to the baseline differences in hypertension, or use of ACE-inhibitors did not provide further understanding of the results.

The approach to management of myocardial ischemia in patients with no obstructive CAD remains unclear. A majority of these patients are women[2], and both short[34] and intermediate-term[29, 32] follow-up indicate a more adverse prognosis[35–37], as well as a high cost for care[38]. Persistent chest pain[39], evidence of coronary endothelial dysfunction[40], and evidence of ischemia[32] in women with no obstructive CAD portend an adverse cardiovascular prognosis that is comparable to that of obstructive CAD. While a number of strategies, including beta blockers but not calcium antagonists[41], L-arginine[42], imipramine[43], and exercise[44] may be associated with symptom relief, no clinical trials to determine the effectiveness of treatment on adverse outcomes have been conducted in this population.

Conclusions

Among postmenopausal women with myocardial ischemia and no obstructive CAD, hormone therapy with 1/10 NA/EE is associated with reduced chest pain symptoms, menopausal symptoms and improved quality of life with trends for improved exercise performance, but not improvement in myocardial ischemia or endothelial function measures. Given that it was not possible to enroll the pre-specified sample size, the results should be interpreted with caution. The efficacy and safety of this type of hormone therapy for symptomatic women in this selected cohort requires prospective trial testing. The current trial results can be used for future sample size estimation.

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The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

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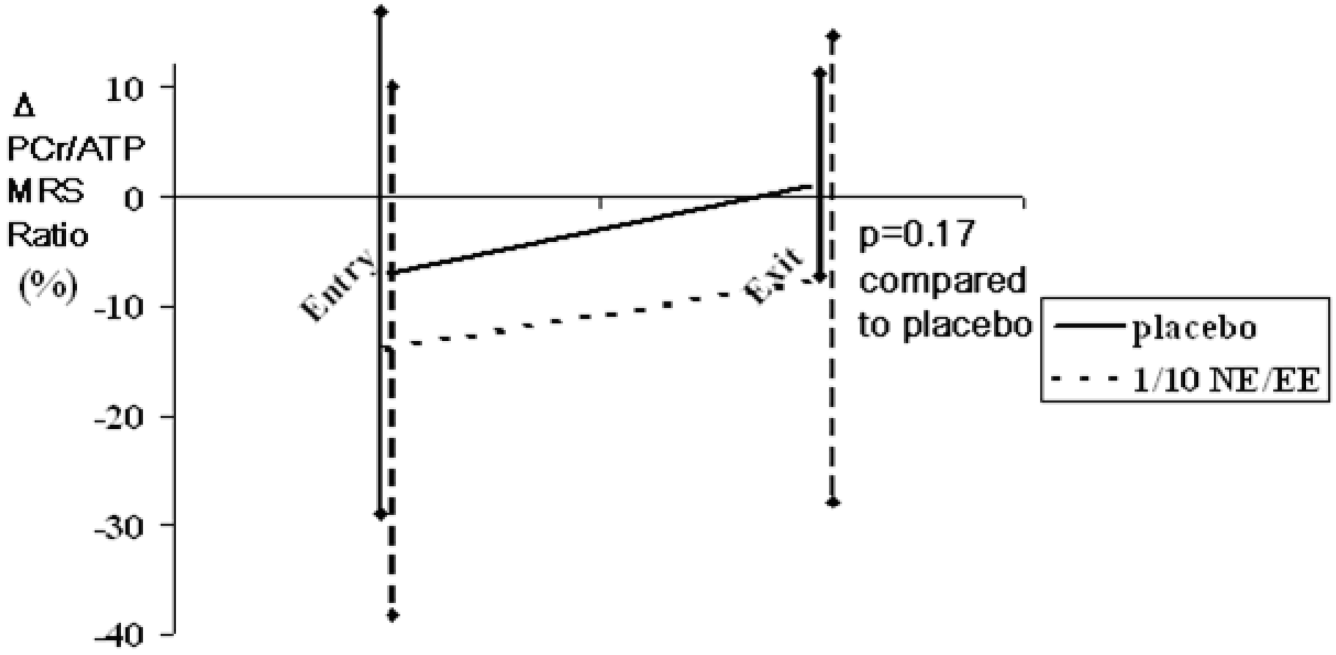

Figure 1.

P-31 gated magnetic resonance cardiac spectroscopy (MRS) reported as change (Δ) in PCr/ATP ratio, with isometric submaximal handgrip stress at study baseline (n=28) and exit (n=26) by treatment in placebo and 1/10 NA/EE groups. Δ PCr/ATP ratio defined as: (stress- [average of rest and recovery periods])/average of rest and recovery periods X 100, and expressed as % mean±SD. For this trial, myocardial ischemia was pre-specified as a fall in quantitative PCr/ATP ratio >20% from rest, and a lower value is considered indicative of greater ischemia.

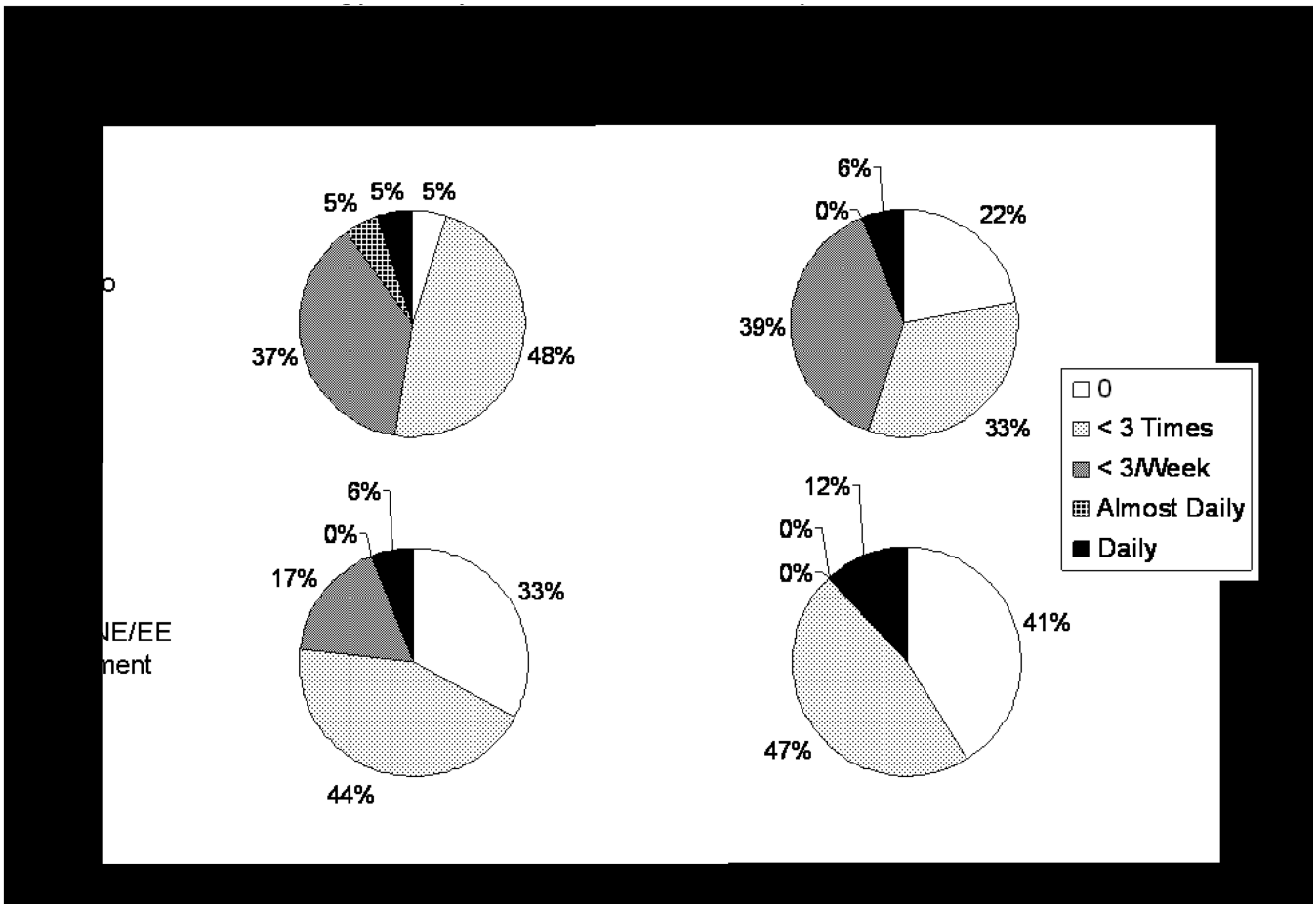

Figure 2.
Chest pain frequency in the last 6 weeks measured at study baseline (n=37) and exit (n=35) according to treatment.

Table 1

Baseline Characteristics by Treatment Assignment

Characteristic	Placebo (n=19)	1/10 NA/EE (n=18)	p value
Age in years (mean ± SD)	59 ± 7	56 ± 9	0.43
Race-nonwhite (%)	16	17	0.99
High School or less (%)	68	56	0.42
Current HT use-prior to entry (%)	42	33	0.58
History Hypertension (%)	72	29	0.01
History Diabetes (%)	26	22	0.77
History Dyslipidemia (%)	39	61	0.18
Current Smoking (%)	11	11	0.99
Total Cholesterol (mg/dl)	205 ± 39	195 ± 47	0.44
HDL-Cholesterol (mg/dl)	54 ± 9	48 ± 16	0.08
LDL-Cholesterol (mg/dl)	124 ± 38	120 ± 51	0.96
Triglycerides (mg/dl)	134 ± 64	132 ± 92	0.62
Systolic Blood Pressure (mmHg)	136 ± 18	130 ± 18	0.47
Diastolic Blood Pressure (mmHg)	78 ± 9	76 ± 13	0.73
Pulse (beats per minute)	76 ± 11	68 ± 8	0.03
Fasting Blood Sugar (mg/dl)	94 ± 20	93 ± 17	0.96
BMI (kg/m^2)	31 ± 7	31 ± 9	0.52
Waist (cm.)	93 ± 15	92 ± 17	0.77

BMI=body mass index; HDL=high density lipoprotein; HT=hormone therapy; LDL=low density lipoprotein; SD=standard deviation

Table 2

Menopausal Symptoms and SF 36 scale at Baseline and Exit by Treatment

	Placebo (n=19)	1/10 NA/EE (n=18)	P	Placebo (n=18)	1/10 NA/EE (n=17)	P
	Baseline			Exit		
Menopause symptoms (%)						
Hot flushes or flashing	68	89	0.23	89	41	0.003
Poor Memory	53	76	0.14	78	59	0.23
Change in Sexual Desire	37	50	0.42	67	35	0.06
Vaginal Dryness	58	44	0.41	67	35	0.06
Avoiding Intimacy	37	39	0.90	56	24	0.05
SF-36 Scale (mean±SD)						
Physical Functioning	43.8 ± 27.4	60.8± 27.5	0.08	44.4± 29.5	59.4± 23.5	0.09
Role-Physical	37.3± 40.2	54.2± 41.3	0.19	25.0± 33.2	58.8± 37.4	0.01
Role- Emotional	66.7± 41.6	70.3± 42.6	0.72	66.7± 39.6	76.5± 34.9	0.42
Bodily Pain	42.1± 17.4	53.3± 21.4	0.09	41.5± 21.6	54.5± 23.6	0.08
General Health	57.4± 15.1	55.4± 19.4	0.67	57.2± 15.8	55.2± 19.7	0.67
Mental Health	65.7± 19.9	66.7± 20.6	0.88	69.3± 18.8	66.4± 19.6	0.78
Vitality	42.9± 20.4	35.6± 23.1	0.31	41.2± 18.0	35.6± 24.5	0.40
Social Functioning	53.2± 24.3	59.4± 14.7	0.48	56.1± 20.6	59.4± 16.0	0.71

Table 3

Menopausal Symptoms and SF 36 scale at Baseline and Exit by Treatment

	Placebo (n=19)	1/10 NA/EE (n=18)	P	Placebo (n=18)	1/10 NA/EE (n=17)	P
	Baseline			Exit		
Menopause symptoms (%)						
Hot flushes or flashing	68	89	0.23	89	41	0.003
Poor Memory	53	76	0.14	78	59	0.23
Change in Sexual Desire	37	50	0.42	67	35	0.06
Vaginal Dryness	58	44	0.41	67	35	0.06
Avoiding Intimacy	37	39	0.90	56	24	0.05
SF-36 Scale (mean±SD)						
Physical Functioning	43.8 ± 27.4	60.8± 27.5	0.08	44.4± 29.5	59.4± 23.5	0.09
Role-Physical	37.3± 40.2	54.2± 41.3	0.19	25.0± 33.2	58.8± 37.4	0.01
Role- Emotional	66.7± 41.6	70.3± 42.6	0.72	66.7± 39.6	76.5± 34.9	0.42
Bodily Pain	42.1± 17.4	53.3± 21.4	0.09	41.5± 21.6	54.5± 23.6	0.08
General Health	57.4± 15.1	55.4± 19.4	0.67	57.2± 15.8	55.2± 19.7	0.67
Mental Health	65.7± 19.9	66.7± 20.6	0.88	69.3± 18.8	66.4± 19.6	0.78
Vitality	42.9± 20.4	35.6± 23.1	0.31	41.2± 18.0	35.6± 24.5	0.40
Social Functioning	53.2± 24.3	59.4± 14.7	0.48	56.1± 20.6	59.4± 16.0	0.71