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Longterm effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease

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Abstract

Objectives: The aim of the present study was to evaluate the effects of HRT on symptoms of angina pectoris, quality of life and factors of importance for compliance in women with ischemic heart disease. *Methods:* Sixty postmenopausal women with coronary artery disease were randomized into three groups: one group received transdermal 17β-estradiol at a dose of 50 μg per 24 h alone for 18 days followed by 10 days of combined treatment with medroxyprogesterone acetate (MPA) 5 mg orally; the second group received placebo and the third group received conjugated estrogens orally for 18 days followed by a combined treatment with MPA for 10 days. Clinical evaluations were performed at baseline, after 3, 6 and 12 months. The investigations included gynecological history, occurrence of climacteric symptoms, quality of life evaluation, cardiac history and symptoms of angina pectoris. *Results:* Forty-six women (77%) completed the study during 1 year. The following cardiac events occurred in the women who completed the study: one patient was hospitalized because of congestive heart failure (patch), two patients because of angina pectoris, one patient because of coronary bypass operation (CEE) and three patients underwent balloon dilatation (placebo), all three on CEE. Among the 14 women who discontinued, two patients had TIA (patch), one experienced palpitations (CEE) and one woman died from myocardial infarction (placebo). Overall improvement in mood and cognitive functions were reported in all three treatment groups. *Conclusions:* HRT does not seem to have negative effects on symptoms of angina pectoris and seems to increase quality of life in older women with coronary heart disease. It also seems safe from the cardiovascular point of view.

Keywords: Hormone replacement therapy; Coronary artery disease; Symptoms of angina pectoris; Quality of life; Compliance

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1. Introduction

One of the earliest positive reports of the effects of estrogen on the cardiovascular system was a study in estrogen depleted female oophorectomized cynomolgous monkeys. They were all on cholesterol-rich diet and those given estrogen replacement therapy developed much less coronary artheromathosis compared with the others [1]. After that, several reports from large observational and epidemiological studies show that hormonal replacement therapy (HRT) to healthy postmenopausal women has beneficial effects on morbidity and mortality in coronary artery disease [2,3]. However, data from randomized prospective placebo controlled studies are still missing. Recent retrospective data has pointed out a slightly increased risk of venous thromboembolism in women using HRT [4–6]. Furthermore, it is well known that HRT has a positive effect on quality of life, such as well-being, vasomotor symptoms, sleeping disturbances and cognitive functions in climacteric women [7,8]. However, to our knowledge nothing is published on the effects of HRT on symptoms of angina pectoris and quality of life as well as on compliance in older women with ischemic heart disease, mainly lacking vasomotor symptoms.

Therefore, the aim of the present study was to evaluate the effects of HRT on symptoms of angina pectoris and quality of life when compared with placebo in women with ishemic heart disease and to investigate factors of importance for compliance. The study was approved by the Ethics Committee of the Karolinska Hospital.

2. Material and methods

2.1. Clinical material and study design

Sixty postmenopausal women with coronary artery disease aged 44–75 years participated in the study. For baseline characteristics, see Tables 1–3. The women were randomized into three treatment groups. No significant differences between the groups were found concerning age, height, weight, BMI and W/H ratio. The women were all overweight. The medication except from the study drugs was equally distributed between the three treatment groups.

Table 1
Some characteristics in 60 women with coronary artery disease

	Treatment			
	Patch TTS E2 50 μg/24h ($n = 20$)	Placebo ($n = 20$)	Tablets CEE 0.625 mg/daily ($n = 20$)	Total ($n = 60$)
Age (years)	58.6 ± 6.3 (47–69)	61.3 ± 7.0 (50–75)	58.3 ± 6.5 (44–68)	59.4 ± 6.7 (44–75)
Height (m)	1.60 ± 0.04 (1.53–1.68)	1.62 ± 0.05 (1.53–1.72)	1.60 ± 0.07 (1.48–1.71)	1.61 ± 0.06 (1.48–1.78)
Weight (kg)	69.1 ± 12.4 (50.0–97.0)	73.2 ± 12.8 (55.0–103.0)	67.4 ± 13.3 (45.0–90.0)	69.1 ± 12.9 (45.0–103.0)
BMI	26.8 ± 4.9 (18.6–37.0)	27.7 ± 5.2 (21.5–40.7)	26.0 ± 4.6 (20.0–38.9)	25.9 ± 4.9 (18.6–40.7)
W/H ratio	0.86 ± 0.12 (0.72–1.31)	0.85 ± 0.05 (0.79–0.96)	0.83 ± 0.05(0.72–0.93)	0.85 ± 0.08 (0.72–1.31)
Years after menopause	9.3 ± 5.9 (1–19)	13.3 ± 7.8 (4–26)	11.6 ± 6.7 (2–23)	11.4 ± 6.9 (1–26)
Smokers				
Former	8	10	9	27
Present	7	5	6	18
Never	5	5	5	15

Mean ± S.D. (range)

Table 2
Diagnoses in 60 women with coronary artery disease

	Treatment Patch ($n = 20$)	Placebo ($n = 20$)	Tablets ($n = 20$)	Total ($n = 60$)
Previous myocardial infarction	10	11	11	32
Previous bypass surgery	7	5	6	18
Previous PTCA (balloon dilatation)	2	7	2	11
Diabetes type I	0	0	1	1
Diabetes type II	3	1	0	4
Hypertension	13	8	5	26
Hyperlipidemia	9	12	10	31
Claudication	5	3	2	10
Migraine	1	3	1	5

2.2. Treatment given

2.2.1. Group one

Transdermal 17β estradiol at a dose of 50 μg per 24 h alone, for 18 days (Estraderm®, Ciba–Geigy, Basel, Switzerland) followed by 10 days of combined treatment with transdermal estradiol and medroxy-progesterone acetate (MPA) (Provera®, Syntex USA) 5 mg orally.

2.2.2. Group two

Transdermal placebo for 18 days followed by 10 days of combined placebo treatment with tablets.

2.2.3. Group three

Conjugated estrogens (CEE) orally for 18 days (Premarina®, Wyeth, Ayerst, Philadelphia) at a dose of 0.625 mg followed by a combined treatment with MPA at a dose of 5 mg daily for 10 days.

2.3. Study design

Clinical evaluations were performed at baseline and after 3, 6 and 12 months of treatment and 4–6 weeks after completion of treatment. The pretreatment investigations included gynecological history and occurrence of climacteric symptoms, gynecological examination, Pap smear and mammography (if not performed within 2 years prior to visit). Venous blood samples were drawn for analyses of estradiol, estrone, estrone sulphate and follicle stimulating hormone at baseline, 3, 6, 12 months and 4–6 weeks after completion of the study. The blood sampling was performed in the estrogen phase 1–4 days before initiation of gestagen therapy. At every visit the patients were asked about their intake of study and other medication. Pretreatment assessment was also performed at the Department of Cardiology, with cardiac history and physical examination, symptoms of angina pectoris were evaluated using the Canadian Heart Association protocol [9]. For quality of life evaluations the Nottingham health profile questionnaires and others evaluated by Wiklund et al. were used [10].

Hormone assays for estradiol determinations were performed using commercial radio immunoassay kits, Eir, Ria 25 and Eir Ria 155 from Radio Isotopic Service, Wurelingen, Switzerland. For determination of FSH commercial kits from Diagnostic Products. (Los Angeles, CA) were used. For estrone and estrone sulphate measurements, the methods by Aedo et al. were used [11].

3. Results

Of the 60 women who were included in the study, 46 (77%) completed the study during 1 year; 14 with transdermal estrogen, 14 treated with transdermal placebo and 18 given oral conjugated estrogens. The following cardiac events occurred in the women who completed the study: one patient was hospitalized due to increased

Table 3
Medication in 60 women with coronary heart disease

	Treatment			
	Patch ($n = 20$)	Placebo ($n = 20$)	Tablets ($n = 20$)	Total ($n = 60$)
Nitrates	12	15	14	41
Beta-blockers	12	15	10	37
Calcium channel blockers	9	6	5	20
Aspirin-warfarin	15	14	15	44
Ace-inhibitors	3	1	3	7
Diuretics	8	6	6	20
Lipid lowering drugs	2	1	9	12
Thyroid drugs	1	2	4	7

congestive heart failure (patch), two because of angina pectoris and one due to coronary by pass operation (CCE) and three patients underwent percutaneous transluminal coronary angioplasty (placebo). Among the 14 women (23%) who discontinued, two patients had TIA (patch), one experienced palpitations (CCE) and one woman died from myocardial infarction (placebo). Other reasons for drop out were: heavy bleedings (tablets; $n = 2$), allergic skin reaction (patch; $n = 1$), peripheral edema (patch; $n = 1$) failure to cooperate (placebo; $n = 4$), severe headache (tablets; $n = 1$) and palpitations (patch; $n = 1$). The levels of FSH, estradiol, estrone and estrone sulphate at baseline and during treatment are shown in Table 4, indicating proper tablet intake and patch use. The effects of differences in dose, administration and type of medication on circulating estrogens and FSH are obvious. The levels of equiline estrogens were not measured. The levels of estrone seem to be lower than those of estradiol during oral intake. This is probably caused by the great variation between individuals and the fact that blood was drawn only at one occasion with varying time after tablet intake.

The effects of treatment on angina pectoris are shown in Tables 5 and 6. The patients were divided into two groups, one with mild (Canadian Heart I–II) and one with moderate to severe (Canadian Heart III–IV) angina pectoris and the change from baseline was recorded. The medication was unchanged throughout the study, except from the intake of nitrates which varied during the study period. No significant difference between the three treatment groups in the occurrence of angina pectoris was seen at baseline and after 6 and 12 months of treatment.

A comparison between self-reported occurrence of positive and negative effects of treatment in those women who completed the treatment and those who dropped out is shown in Table 6. Positive and negative effects of treatment occurred among both the women who continued treatment and among those who dropped out, as well as among estrogen and placebo treated women. The only exception was bleeding irregularities. The number of patients was too small for statistical comparisons.

3.1. Evaluation of the quality of life forms gave the following results

A significant improvement compared with baseline in depressed moods ($P \leq 0.054$) was found only in the tablet group. Overall improvement in mood (more vital than before, more harmonic than before) was reported by all three treatment groups ($P < 0.027$) without significant differences between groups. Cognitive functions were significantly improved in all three groups ($P < 0.03$) including placebo. No improvement in sleeping disturbances (including problems to get to sleep and waking up during the night) was found. Among the women treated with estrogen tablets, nine reported vasomotor symptoms (sweating and hot flushes) at baseline. After 1 year five women

Table 4
Hormonal status at baseline and after 6 and 12 months of treatment

	Patch			Placebo			Tablets		
	Baseline	6 months	12 months	Baseline	6 months	12 months	Baseline	6 months	12 months
Follicle-stimulating hormone									
FSH (IU/l)	34 ± 12 (5–54)	20 ± 8 (1–36)	22 ± 10 (1–35)	46 ± 24 (19–102)	43 ± 20 (22–98)	37 ± 15 (5–62)	48 ± 20 (23–96)	30 ± 20 (5–107)	25 ± 10 (5–40)
Estradiol									
E_2 (pmol/l)	137 ± 126 (44–509)	205 ± 76 (99–421)	182 ± 68 (91–325)	89 ± 36 (33–165)	95 ± 35 (39–164)	106 ± 63 (41–282)	83 ± 31 (26–133)	358 ± 280 (68–1186)	386 ± 301 (115–1174)
Estrone									
E_1 (pmol/l)	195 ± 100 (81–431)	207 ± 53 (124–300)	205 ± 54 105–295)	171 ± 60 (85–271)	163 ± 57 (81–275)	186 ± 127 (61–549)	154 ± 48 (64–247)	332 ± 141 (157–640)	334 ± 128 (154–602)
Estrone sulphate									
E_1S (nmol/l)	2.22 ± 1.02 (2.21–4.55)	2.82 ± 1.45 (< 1.34–6.8)	2.62 ± 1.42 (<1.34–6.39)	—	—	—	1.78 ± 0.66 (0.75–3.54)	8.57 ± 6.85 (2.26–28.1)	7.89 ± 5.34 (1.46–21.00)

Mean ± S.D. and (range)

Table 5
Symptoms of angina pectoris in 46 women during treatment; *n*

Angina pectoris	Treatment groups								
	Patch			Placebo			Tablets		
	I[a]	Ii[b]	III[c]	I[a]	II[b]	III[c]	I[a]	II[b]	III[c]
Mild	13	12	13	11	11	10	14	14	16
Severe	1	2	1	3	3	4	4	4	2
Total	14	14	14	14	14	14	18	18	18

[a] I = baseline; [b] II = 6 months; [c] III = 12 months.

still experienced vasomotor symptoms of whom four reported improvement and one worsening of symptoms. In the patch group, seven women suffered from vasomotor symptoms at baseline, after 1 year only one reported improvement. In the placebo group, nine women had vasomotor symptoms at baseline and 11 after 1 year.

4. Discussion

This is the first prospective relatively long-term randomized study, where the effects on angina pectoris, compliance and quality of life in postmenopausal women with coronary artery disease has been studied. Sixty women were randomized to either estrogen patch, estrogen tablets or conventional medium potent doses. Gestagen was added for 10 days of each 28 day treatment period. All patients suffered from rather advanced coronary artery disease and 70% had symptoms of angina pectoris at baseline. No harmful effects on angina pectoris were induced by HRT as compared with placebo during 12 months treatment. One would have expected positive effects of HRT on angina pectoris, because of positive case reports [12]. In our study a positive effect might have been masked by the actions on the arterial wall of the comprehensive mediation (nitrates, beta-blockers, calcium-channel blockers, etc.). Against this points the fact that no change took place in medication during the year.

In women suffering from Syndrome-X (i.e. angina pectoris positive exercise test and normal coronary angiogram) addition of estrogen to the treatment has recently been shown to relieve breast pain [13,14]. Furthermore, it has been reported that estrogens might have antiischemic properties, inducing longer exercise time and less ST-segment depression in the exercise test situation [15]. There was no worsening of the cardiac status on the whole, or of symptoms of angina pectoris in the estrogen treated women compared with placebo. Among the few patients who experienced adverse cardiac events during the study year, very few were associated with HRT. The only death case (myocardial infarction) was treated with placebo. In the two cases of TIA, it is uncertain whether they were related to HRT.

Compliance was evaluated in relation to positive and negative effects of treatment. Positive effects were increased well-being and cognitive functions. Negative side effects were bleeding irregularities and negative mood. Both negative and positive effects were seen in the placebo group, except for irregular bleedings Table 7.

It was desirable to test both 17β-estradiol and conjugated estrogens since 17β-estradiol is the most used preparation for postmenopausal substitution therapy in Europe, while conjugated estrogens are most commonly used in USA. Standard doses were used in this study. Forty-six women (77%) completed the study during one year in spite of several negative side effects. Forty-two women wished to continue HRT after the study and 18 of those preferred continuous combined treatment in order to avoid withdrawal bleedings. In a review [16], withdrawal bleedings were reported as a main reason for drop out. In one study, it was found that compliance was higher

Table 6
Change in symptoms of angina pectoris during treatment in 46 women; *n*

Treatment groups	Symptoms								
	Better			Unchanged			Worse		
	I[a]	II[b]	III[c]	I[a]	II[b]	III[c]	I[a]	II[b]	III[c]
Patch	2	1	2	10	12	11	2	1	1
Placebo	7	3	7	5	9	5	2	2	2
Tablets	5	6	6	10	9	10	3	3	2

[a] I = from baseline to 6 months; [b] II = from 6 months to 12 months; [c] III = from baseline to 12 months.

among women who used continuous combined treatment than in women receiving sequential therapy. In two other studies [17,18], continuous combined treatment was suggested as an alternative in order to achieve strong long-term compliance. To our knowledge no studies on compliance with HRT have been performed in women more than 10 years post menopause.

Concerning quality of life, only minor improvements were found between treatment groups and over time. This is probably due to the small number of participants and that most patients did not suffer from vasomotor symptoms. In a study without a placebo group, the effects of transdermal estrogens on quality of life was followed and women with few complaints prior to treatment did not report improvement by treatment [8]. This is in accordance with our findings. However, the improvements in well-being and cognitive function did not differ between estrogen treated women and placebo in our study, while depressed mood was significantly improved only in the tablet group, which suggests that the higher dose of estrogens might be of importance. The other findings could as well be due to the good care taking in all groups of the patients as to the hormone treatment.

In order to evaluate the true cardiovascular and quality of life the effects of estrogen replacement therapy in older postmenopausal women with cardiovascular disease prospective longitudinal studies involving large numbers of women are needed.

In conclusion, it seems that hormonal replacement therapy does not have negative effects on symptoms of angina pectoris and seems to increase quality of life in older women with coronary heart disease. It also seems safe from the cardiovascular point of view.

Table 7
Effects of treatment in 46 patients who completed (A) the study and in 14 patients who discontinued (B) before one year; *n*

	Treatment groups					
	Patch		Placebo		Tablets	
	A ($n = 14$)	B ($n = 6$)	A ($n = 14$)	B($n = 6$)	A ($n = 18$)	B ($n = 2$)
Increased well-being	6	2	2	1	8	0
Mucous membrane changes	1	1	2	0	6	1
Release of climacteric symptoms	4	1	1	0	4	1
Breast tenderness	4	0	1	1	7	1
Negative mood changes	7	2	2	0	2	0
Headache	0	0	3	0	3	0
Bleeding irregularities	7	2	0	0	3	0
Allergic patch reaction	1	1	5	1	—	—

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