Coronary heart disease and hormone replacement therapy – from primary and secondary prevention to the window of opportunity

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Abstract

The aim of this work is to give summary of changes in recommendation for hormone replacement therapy (HT) and cardiovascular prevention during last decade. Conclusions from observational studies demonstrated a positive effect of HT in both the primary and secondary prevention of coronary heart disease (CHD). But large randomized trials failed to prove this positive effect; on the contrary, the cardiovascular risk was increased in the beginning of therapy. But estrogen arm of Women's Health Initiative (WHI) show neutral influence and the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) indicate possible positive effects of some HT regimens. Also reanalysis of WHI in age-related groups show the window of opportunity. The prevention of CHD was excluded from possible indications of HT. Many questions regarding optimal choice in the individual treatment strategies have been raised.

HT in its individualized form remains the first choice therapy for the acute climacteric syndrome, for the prevention and the therapy of urogenital atrophy and prevention of osteoporosis. Early start of HT has neutral or slightly positive effect on cardiovascular prevention.

Abbreviations:

CEE	- conjugated equine estrogens
CHD	- coronary heart disease
ELITE	- Early versus Late Intervention Trial with Estradiol
EPAT	- Estrogen in the Prevention of Atherosclerosis Trial
ET	- estrogen replacement therapy
ESPRIT-UK	- Oestrogen in the prevention of the Terinfartion Trial
EVTET	- Estrogen in Venous Tromboembolism Trial
HERS	- Heart and Estrogen/progestin Replacement Study
HT	- hormone replacement therapy
KEEPS	- Kronos Early Estrogen Prevention Study
MPA	- medroxyprogesteronacetate
PEPI	- Postmenopausal Estrogen/Progestin Interventions
RR	- relative risk
WHI	- Women's Health Initiative
WISDOM	- Women's International Study of Long Duration Oestrogen After Menopause

ORIGINAL ARTICLE

INTRODUCTION

Outstanding results of observational population and clinical studies led to an exaggerated image of the hormone replacement therapy (HT) for postmenopausal women as a panacea. The greatest hopes have been pinned on a possible prevention of coronary heart disease (CHD) through HT.

Several minor studies published between 1987 and 1991 showed protective influence of HT (Gruchow *et al.* 1988, Henderson *et al.* 1991). Studies confirmed positive influence on the lipid profile (Walsh 1991), distribution of the subcutaneous fat (Haarbo 1991), vasodilatation (Pines *et al.* 1992) and moderate hyperhomocysteinemia (Van de Mooren 1995).

The importance of the structure and way of application of HT was indicated in several studies. Adding progestin leads to a slump of positive effects of estrogens on the lipid profile proportionately to its androgenicity. Per oral estrogens cause increased synthesis of triglycerides. Transdermal estrogens decrease the level of triglycerides or do not exhibit any effects (Mueck 2012, Fait *et al.* 2006a, Fait *et al.* 2008).

OBSERVATIONAL STUDIES

Already in 1987, it was clear from the summary of population studies (Colditz 1987) that the total relative risk (RR) of CHD in connection with estrogen replacement therapy (ET) fell to 0.6. By metanalysing epidemiologic studies carried out before 1995 (Grodstein & Stampfer 1996) we find out that the RR for users of HT was 0.65 and even 0.49 for current users in comparison with women who had never used HT.

The fact of positive influence of HT on the risk of CHD appears inconvertible in the light of the results of the observational study Nurses´ Health Study published in 1996 (Grodstein 1996). According to that prospective study of 121,700 married nurses realised through questionnaires sent every two years, HT reduces the risk of CHD for healthy women independently on the length of administering or the dose of estrogen. The RR is 0.39 for current users of combined HT or 0.60 for users of ET. There is an apparent difference between current (RR 0.37) and formal (RR 0.96) users. After adjusting with regard to the age, the RR is 0.6 for current users and insignificant improvement of the RR to 0.8 for former users.

As well as in secondary prevention, significant reduction of risk of progression of CHD (Henderson *et al.* 1991, Newton 1997) for women with case history of myocardial infarction using estrogens (RR of 0.5 for current users and 0.6 or 0.8 for former users) has been proved. Schlipak *et al.* (2001) found out in a group of 114,724 women hospitalized for myocardial infarction with a prevalence of using HT of 6.4% a significantly higher survival rate of HT users (death rate of 7.4% in comparison with 16.2%) with death RR of 0.41.

INTERVENTION STUDIES

HERS study wanted to verify the effect of HT in secondary prevention of CHD (Hulley *et al.* 1998). It was a randomized double-blind prospective study including two groups of 1,380 women with CHD whose average age was 67 which is fairly high. Combination of 0.625 mg CEE + 2.5 mg MPA was continuously administered to one group, while placebo was administered to the other.

In the course of the duration of the study (4.1 years) incidence of heart attack did not decline within the medicated group. In the first year of the duration of the study even more heart attacks occurred within this group than within the placebo group. Fewer ones occurred only in the 4th year of monitoring. Furthermore, there were increased risks of thrombo-embolic disease (RR of 2.89), gall bladder disease (RR of 1.38) and breast cancer (RR of 1.3). The risk of coronary stroke falls during the first year in four-months periods form RR of 2.29 to 1.46 and finally to 1.18. A zero to negative effect of HT in secondary prevention of CHD contrasts with positive influence to of the lipid spectrum (reduction of LDL-cholesterol by 11% and increase of HDL-cholesterol by 10%)

One of the theories explains the negative result by destabilising the atherosclerotic plaque due to administering HT (Fait *et al.* 2006b). In the PEPI study (Writing Group for the PEPI Trial 1995) administering HT perorally significantly increased the level of C-reactive protein that is a marker of instability. Based on the results, the authors do not recommend starting HT within secondary prevention of CHD.

Expected significant reduction of the risk with HT users did not occur by extending the monitoring period to 6.8 years in the HERS II study (Mendelsohn & Karas 2001) either. Nor a supplementary re-analysis of the HERS study results in 86 symptoms identified a subgroup of participants for whom the HT would be unambiguously beneficial (Furberg 2002).

Both the results of HERS and re-analyses give always the same information. It is not useful to start a hormone replacement therapy 10–20 years after the menopause in quest of secondary prevention of ICHS.

Women´s Health Initiative study (WHI) (Rossouw *et al.* 2002) was presented as one of long-awaited studies o the influence of HT on primary prevention of CHD. The study processed in 1993–1998 included women 50–79 year old at least 6 months after their menopause. 26% of women who had already used HT were included after at least three-month break in the therapy. The study had two basic arms – ET for women after hysterectomy and a combined estrogengestagenic therapy for women with a uterus.

The line of the study with a combined HT composed of 0.625 mg CEE and 2.5 mg MPA was prematurely terminated after 5.2 years of duration because of prevailing negative effects of the therapy over placebo. Within the group of 8,506 users and 8,102 examinations, increased

risks of breast cancer with the RR of 1.26 (95% CI: 1.00–1.59), CHD with the RR of 1.29 (95% CI: 1.02–1.63), vascular brain strokes with the RR of 1.41 (95% CI: 1.07–1.85) and thromboembolism with the RR of 2.13 (95% CI: 1.26–3.55) were identified. Preventive influence on femoral neck fracture with the RR of 0.66 (95% CI: 0.45–0.98), endometrial cancer with the RR of 0.83 (95% CI: 0.47–1.47) and colorectal cancer with the RR of 0.63 (95% CI: 0.43–0.92) is not enough to balance the negatives in this study. Other factors connected with estrogen deficit (urogenital atrophics, quality of life of the patient, subjective satisfaction) were not discovered.

Even the estrogenic arm of the WHI study was terminated prematurely after 6.8 (5.7–10.7) years with the reason that further continuation did not bring new data, no set risk limits had been exceeded but the risk of CHD did not decrease. The study is very well randomized and all its arms are fully comparable. However, the presentation of the group that may present normal Northern American population as a group of healthy women is surprising. For starting primary prevention of CHD the average age of 63.2 appears to be rather advanced and a high proportional occurrence of factors influencing CHD (34% with BMI >30, 50% abuse of nicotine, 4.4% of diabetics, 6.9% of hypolipidemics users, 20% of Aspirin users) and the anamnesis of CHD itself (4.4%) is striking.

Beral *et al.* (2002) sums up the results of HERS, WHI, WEST and EVTET – all prospective studies with more than 20,000 women using placebo, monitored for 4–9 years without identifying any significant changes for CHD.

THERAPEUTIC WINDOW THEORY

The main difference between HERS and WHI studies on one side and previous studies on the other side was the fact that occurrence of acute climacteric syndrome was not their inclusion criterion. The syndrome is in clinical practice absolutely predominant indication to HT. The aim of HERS and WHI studies was not to prove again great effect of HT on symptoms of acute climacteric syndrome but to clarify whether it would be appropriate to do area prevention of CHD by applying estrogens in women after menopause. The answer is no.

Even a question of cardiovascular safety emerged and here a positive answer is given by studies or reanalyses of studies monitoring women in normal indicative age for HT. If the process of atherogenesis has not developed, it is possible to prevent it by estrogens substitution but it is necessary to start the HT as soon possible after the menopause.

The importance of correct timing of HT was shown by the analysis of Nurse's Health Study (Grodstein *et al.* 2006) and by the meta-analysis of 30 randomized studies carried out between 1966 and 2002 including 26,708 women. It showed that HT had reduced total mortality in the group less than 60 years of age but not in older women. HT did not influence deaths of cardiovascular diseases or tumours but only deaths of different causes (Salpeter *et al.* 2004).

The trend of importance of correct timing of HT was monitored even by an extensive re-analysis of WHI according to age groups, time span between the start of the therapy and the menopause and occurrence of the acute climacteric syndrome. Hormone replacement therapy – in the WHI study – does not reduce the risk of CHD but after adjusting according the risk factors we may claim that the risk is lower for ET than for combined HT (p=0.02). In the age group of 50–59, the risk of CHD in HT (Table 1) (Rossouw *et al.* 2007) does not increase unlike older age groups.

The EPAT study monitored the effect of 1 mg of estradiol on the thickness of carotids. Condition for including into the study was absence of intima-media widening (thus really in primary prevention) and normal or medically adjusted values of the lipid spectrum. 222 women older than 45 year were included; measurements were made for two years every six months. In the group of women using estradiol the progression of subclinical atherosclerosis was lower

Tab. 1. Reanalysis of WHI study by age and years from menopause: CHD risk.

group (drug/placebo)	years	RR (95%CI)
HT (13,816 / 13,531)		**1.07 (0.92–1.23)**
age at start	50–59	0.93 (0.50–1.33)
	60–69	0.98 (0.79–1.21)
	70–79	1.26 (1.00–1.51)
years from menopause	<10	0.76 (0.5–1.16)
	10–19	1.1 (0.84–1.45)
	≥20	1.28 (1.03–1.58)
CEE (5,310 / 5,429)		**0.95 (0.78–1.16)**
age at start	50–59	0.63 (0.36–1.09)
	60–69	0.94 (0.71–1.24)
	70–79	1.13 (0.82–1.54)
years from menopause	<10	0.48 (0.2–1.17)
	10–19	0.96 (0.64–1.44)
	≥20	1.12 (0.86–1.46)
CEE + MPA (8,506 / 8,102)		**1.23 (0.99–1.63)**
age at start	50–59	1.29 (0.79–2.12)
	60–69	1.03 (1.03–1.43)
	70–79	1.48 (1.04–2.11)
years from menopause	<10	0.88 (0.54–1.43)
	10–19	1.23 (0.85–1.77)
	≥20	1.66 (1.14–2.41)

by 0.0017 mm per year in comparison with placebo (+ 0.0037 mm per year). This difference was not obvious in the group of women using hypolipidemics (Hodis *et al.* 2008).

The WHI-CAC study (Coronary Artery Calcification) followed up with the estrogenic arm of WHI where a group of 1,064 women put on therapy in the age of 50–89 after 7.4 years of using ET had CT (computer tomography) of the heart measuring the score of calcium in the vascular wall of coronary vessels. It proved reduced deposition of calcium in the vascular wall with ET and thus moved provably safe age of use to 65 (Allison *et al*. 2008).

Considerable increase of cardiovascular risk in menopausal women was the impulse for repeated meetings between the European Heart Society and the International Menopause Society leading to a published consensual position: HT in perimenopausal women reduces vasomotor symptoms and improves the quality of life. There is not convincing evidence that such treatment would increase the risk of breast cancer. In older women, the cardiovascular risk of HT exceeds its assets; therefore HT should not be used in primary or secondary prevention of CHD. When treating younger symptomatic women, assets should be evaluated in comparison with the risks of the therapy (Collins *et al.* 2007).

Further data may be brought by ESPRIT-UK, ELITE, KEEPS and WISDOM studies monitoring cardiovascular risks of early started HT (Rosano *et al.* 2012; Hodis *et al.* 2012).

Observational studies indicated relative strong positive effect of HT on both primary and secondary prevention of CHD. Despite their load by the bias phenomenon, their results were generalized for the whole population and estrogen was presented as a universal medication and means of prevention. Double-blind randomized placebo-controlled intervention studies as a golden standard of evidence based medicine have not backed that idea.

In 1998, the HERS study rebutted the effectiveness of HT in secondary prevention of CHD. In 2002, the WHI study contested its effectiveness in primary prevention. Studies did not find a new contraindication. Reanalyses and other studies have shown that it is possible to count on primarily preventive effect of HT only in case of its early start.

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