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NEWS AND VIEWS

Is transdermal menopausal hormone therapy (MHT) associated with an increased cardiovascular risk?

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Summary

The US-American Women's Health Initiative Observational Study (WHI-OS) is a prospective cohort study in postmenopausal women aged 50–79 at study entry ($n = 93{,}676$). Annual follow-up was performed by mailed self-administered questionnaires including questions on menopause hormone therapy (MHT). The aim of the present analysis was to compare the impact of various MHT formulations and route of delivery on incident cardiovascular diseases (CVD) [1]. Therefore, only current MHT users were included ($n = 41{,}721$; 45 % of total cohort). MHT subgroups were defined as follows: (1) oral low-dose conjugated equine estrogens (CEE) (<0.625 mg/day), (2) oral standard-dose CEE (0.625 mg/day), (3) oral high-dose CEE (>0.625 mg/day), (4) oral estrogens [CEE or estradiol (E2)], (5) oral estrogen plus progestogen therapy (EPT) (oral CEE or E2 plus progestin or progesterone), and (6) transdermal E2 therapy (ET) of any dosage plus oral progestin or progesterone in women with an intact uterus. Study endpoints were (1) major coronary heart disease (CHD) (nonfatal myocardial infarction, coronary death), (2) stroke, (3) CVD mortality, (4) total CVD (major CHD, stroke, CVD mortality), and (5) all-cause mortality. All analyses (Cox proportional hazards model) were adjusted for established CVD risk factors as well as for time since menopause (<10 vs. ≥10 years), and duration of MHT use (<5 vs. ≥5 years), respectively.

The mean duration of follow-up was 10.4 years. The majority of women used oral CEE ($n = 29{,}944$), mostly as a standard-dose preparation (82 %) and without a combined progestogen (55 %). In contrast, use of oral E2 ($n = 3{,}024$) or transdermal E2 ($n = 2{,}187$) was much less common. However, the exact sample sizes of subgroups for different oral/transdermal E2 dosages, and for E2 with or without a progestogen, respectively, were not provided. The main findings are summarized in Table 1. Time since menopause and duration of MHT use did not have an impact on cardiovascular risks. Absolute CVD risks and all-cause mortality were lower in MHT user close to menopause (no p-level provided). The authors concluded that (1) estrogen dosage, route of delivery and type of estrogen only had a minor impact on CVD risk, however, (2) oral E2 might be associated with a lower risk of stroke, and (3) transdermal MHT and oral low-dose CEE might be associated with a lower risk of CHD compared to oral standard-dose CEE.

Background

Cardiovascular diseases are the main cause of death in women. Thus, any contributing risk factor should be avoided if possible. MHT is considered the most effective treatment for vasomotor symptom relief in postmenopausal women [2]. However, several studies have shown an increased CVD risk within the first year of MHT initiation [3–7]. The standard estrogen and progestogen used in those trials were oral CEE and medroxyprogesterone acetate (MPA), respectively. Furthermore, the majority of trials chose oral CEE at a dosage of 0.625 mg/day considered as standard-dose CEE today. Due to the initial CVD risk increase when starting oral MHT, the question arose if type of estrogen, route of delivery and estrogen dosage may have an impact on CVD risk. An alternative estrogen type is estradiol (E2), transdermal

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Table 1 Comparison of various MHT formulations on cardio- and cerebrovascular risk

Reference	Comparator	Results
Oral MHT (= standard-dose CEE ± progestogen)	Transdermal MHT (= E2 at any dosage ± progestogen)	In favor of transdermal MHT: non-significant risk reduction for all CVD endpoints (most pronounced for major CHD: HR 0.63, 95 % CI 0.37–1.06) but not for all-cause mortality
	Oral low-dose MHT (= low-dose CEE ± progestogen)	In favor of low-dose MHT: Non-significant risk reduction for major CHD, total CVD and CVD mortality but not for stroke and all-cause mortality
	Oral MHT containing E2 (= oral E2 at any dosage ± progestogen)	In favor of MHT containing E2: non-significant risk reduction of stroke (HR 0.64, 95 % CI 0.40–1.02) but no impact on other endpoints
Oral standard-dose CEE alone	Oral combined MHT (= CEE/E2 ± progestogen)	No significant difference for any endpoint

CEE conjugated equine estrogens, *E2* estradiol, *MHT* menopause hormone therapy, *CVD* cardiovascular disease, *CHD* coronary heart disease, *low-dose* <0.625 mg CEE/day, *standard-dose* 0.625 mg CEE/day

patches and gels are an alternative route of delivery, and nowadays various estrogen dosages are available ranging from high-dose, standard-dose, low-dose to ultralow-dose estrogen [8]. Possibly, physiological E2 has a better pharmacodynamic and pharmacokinetic profile compared to CEE, a complex of multiple biologically active estrogens [9]. The advantage of transdermal estrogen application is avoiding the hepatic first-pass-effect causing a pro-coagulant state [10, 11]. And finally, the effect of estrogens on CVD risk might be dose-dependent, possibly making the lowest dosage the safest one.

So far, there are two large-scale trials investigating the impact of estrogen dosage and route of delivery on risk of stroke [12, 13]. First, in a population-based nested case–control study comparing 15,710 stroke survivors with 59,958 controls, transdermal estrogen therapy did not reveal an increased risk of stroke for up to an estrogen dosage of 50 μg/day (adjusted RR 0.81, 95 % CI 0.62–1.05), while oral low- and standard-dose estrogen therapy increased the risk of stroke appreciably (adjusted RR 1.28, 95 % CI 1.15–1.42) even after thorough adjustment for known risk factors for stroke [12]. Second, in comparison to never MHT user, a prospective cohort study, the Nurses' Health Study, found a significantly increased risk of stroke in postmenopausal women using oral standard- (adjusted RR 1.54, 95 % CI 1.31–1.81) or high-dose CEE (adjusted RR 1.62, 95 % CI 1.23–2.14) but not in those using oral low-dose CEE (adjusted RR 0.93, 95 % CI 0.62–1.40) [13]. There are only few larger studies investigating the impact of estrogen formulation on ischemic heart disease. First, in a population-based nested case–control study comparing 1,013 myocardial infarction survivors with 5,000 controls MHT was shown to reduce the risk of myocardial infarction regardless of route of delivery (oral estrogens: adjusted OR 0.66; 95 % CI 0.50–0.88, and transdermal E2: adjusted OR 0.75; 95 % CI 0.47–1.21) [14]. Similarly, in the second population-based nested case–control study comparing 4,537 myocardial infarction survivors with 27,220 controls current and past MHT use was associated with a decreased risk of myocardial infarction regardless of route of delivery (oral MHT: adjusted OR 0.77, 95 % CI 0.66–0.90, and transdermal MHT: adjusted OR 0.66, 95 % CI 0.49–0.88) [15]. The Danish Sex Hormone Register Study (DaHo RS), a prospective cohort study, found a neutral effect on risk of myocardial infarction for any current MHT use (RR 1.03, 95 % CI 0.95–1.11). Subgroup analysis revealed a significantly lower risk with transdermal route of delivery compared to oral unopposed estrogen therapy ($p = 0.04$) [16].

There are two not yet published RCT in postmenopausal women addressing the impact of 5 years of treatment with different estrogen types and route of delivery on surrogate markers of cardiovascular health with carotid media–intima-thickness (CIMT) progression as primary endpoint. The RCT Kronos Early Estrogen Prevention Study (KEEPS) compares the impact of low-dose oral or transdermal E2 with placebo in recently postmenopausal women, respectively [17]. The RCT Early versus Late Intervention Trial with Estradiol (ELITE) compares the impact of oral low-dose E2 (± micronized progesterone) with placebo in either early or late postmenopausal women, respectively (ClinicalTrials.gov Identifier: NCT00114517). So far, preliminary results have been presented at international conferences on menopause revealing either a positive (ELITE; International Menopause Society, Cancun 2014), or neutral (KEEPS; North American Menopause Society, Orlando 2012) effect of E2 on CIMT progression in early postmenopausal women, respectively. In both trials, risks of coronary and cerebrovascular disease were not increased in MHT user.

Comment

This prospective cohort study, WHI-OS, is the largest study to date investigating the impact of different estrogen types, route of delivery and estrogen dosages on various single

and combined cardiovascular endpoints. However, despite the large sample size and long duration of follow-up, the present WHI-OS analysis may not give a definite statement on whether or not transdermal and low-dose MHT display a more beneficial cardiovascular profile than oral or standard-dose MHT, respectively. First, due to the observational nature of the WHI-OS, selection bias through allocation of transdermal estrogen to women at risk for CHD and stroke cannot be excluded and would mitigate any result in favor of the transdermal route. Secondly, sample sizes of women using transdermal MHT ($n = 2{,}187$), and oral low-dose CEE ($n = 2{,}149$) were quite small. Accordingly, subgroup analysis for different E2 dosages in transdermal MHT or progestogen type in combined MHT would not have been reliably possible. Next, risk assessment for each endpoint was based on baseline MHT use. Thus, the analysis did not account for possible modifications of MHT formulation during follow-up. Finally, the study only included current MHT user. However, previous studies have shown an increased cardiovascular risk within the first year after MHT initiation, especially for oral estrogens. Thus, the increased incidence of cardiovascular events within the first year of MHT use may have been missed which may lead to an underestimation of the prevalence of cardiovascular events. In conclusion, the WHI-OS provides further hints for a safer cardiovascular profile of transdermal MHT. Data from RCTs like KEEPS will hopefully add more profound information.

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