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The timing hypothesis: Do coronary risks of menopausal hormone therapy vary by age or time since menopause onset?☆,☆☆

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ABSTRACT

The Women's Health Initiative (WHI), a landmark randomized trial of menopausal hormone therapy (HT) for prevention of chronic disease in postmenopausal women aged 50–79, established that such therapy neither prevents coronary heart disease (CHD) nor yields a favorable balance of benefits and risks in such women as a whole. However, a nuanced look at the data from this trial, considered alongside other evidence, suggests that timing of HT initiation affects the relation between such therapy and coronary risk, as well as its overall benefit–risk balance. Estrogen may have a beneficial effect on the heart if started in early menopause, when a woman's arteries are likely to be relatively healthy, but a harmful effect if started in late menopause, when those arteries are more likely to show signs of atherosclerotic disease. However, even if HT-associated relative risks are constant across age or time since menopause onset, the low absolute risk of CHD in younger or recently menopausal women translates into low attributable risks in this group. Thus, HT initiation for relief of moderate to severe vasomotor symptoms in early menopausal patients who have a favorable coronary profile remains a viable option.

1. Introduction

Menopausal hormone therapy (HT) has long been a mainstay of treatment for vasomotor symptoms of menopause, providing relief from the hot flashes and night sweats that affect many women during this stage of life [1]. Until the early 2000s, HT was also promoted as an effective strategy for preventing coronary heart disease (CHD) and other chronic diseases of aging in postmenopausal women of all ages, particularly those at elevated coronary risk, and was increasingly taken for this purpose [2]. This practice was unwise given the absence of conclusive data from large-scale randomized clinical trials on the balance of risks and benefits of HT used for chronic disease prevention.

Results from the large Women's Health Initiative (WHI) HT trials, the first of which were published in 2002 [3], and smaller trials have now shown that the risks of such therapy outweigh the benefits for many women [1]. In response, the prevalence of HT use in the U.S., which peaked at >40% in 2001, declined sharply [4,5]. However, a closer look at the clinical trial findings indicates that it may be possible to identify women who are most likely to experience a favorable

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benefit–risk balance from HT when it is taken for a currently approved indication—treatment of moderate to severe vasomotor symptoms of menopause, and, in women at high fracture risk who cannot tolerate other therapies, prevention of osteoporosis [6]. This article reviews the evidence from WHI and other randomized trials suggesting that women who are younger or more recently menopausal at HT initiation have more favorable coronary outcomes than their counterparts who are older or further past the menopausal transition—a theory that has been dubbed the 'timing hypothesis.' We also address non-human primate research testing this hypothesis.

2. Overview of the WHI HT trials

In the WHI HT trials, 27,347 healthy postmenopausal women aged 50–79 were randomized to oral estrogen (conjugated equine estrogens [CEE], 0.625 mg/d)—taken with or without oral progestin (medroxyprogesterone acetate [MPA], 2.5 mg/d) depending on hysterectomy status—or to placebo. Because progestin is known to counteract the elevation in endometrial cancer risk conferred by unopposed estrogen therapy, participants with an intact uterus (n = 16,608) were enrolled in the estrogen–progestin trial [3], whereas participants with hysterectomy (n = 10,739) were enrolled in the estrogen-alone trial [7]. At enrollment, 32.3% of participants were aged 50–59 years, 42.2% were aged 60–69 years, and 22.5% were aged 70–79 years; the mean age was 63 years. The sample sizes were chosen to have sufficient power to detect an effect of HT on CHD (defined as nonfatal myocardial infarction [MI] or coronary death), should such an effect exist, and to assess the balance of benefits and risks over an 8.5-year treatment period [8]. However, both trials were stopped early—the estrogen–progestin trial after a median of 5.6 years of treatment because of a significant increase in breast cancer risk and an unfavorable benefit–risk balance in the overall cohort [3], and the estrogen-alone trial after a median of 7.2 years because of an elevated stroke risk that was not counterbalanced by a reduced CHD risk [7]. After the trials were stopped, the participants were followed observationally to determine whether and how quickly treatment effects dissipated. Unless noted, the WHI results reported here are from a comprehensive overview of the findings published in 2013 by WHI investigators [9], or related publications [1,10].

3. HT-associated Health Outcomes in the Total WHI Study Population

Table 1 shows the associations between HT and health outcomes in the WHI study population as a whole.

3.1. *Cardiovascular Disease*

Compared with those randomized to placebo, women randomized to 5.6 years of estrogen–progestin were 18% more likely to develop CHD, although this increase did not reach statistical significance. During the trial's first year, there was a significant 80% risk elevation, which tapered off with time on treatment (p, trend by time = 0.03). Women randomized to 7.1 years of estrogen alone experienced neither an increase nor a decrease in CHD risk. This pattern of results was similar for total MI. Neither HT regimen affected risk of coronary revascularization. Women randomized to estrogen–progestin or estrogen alone were about 35% more likely to suffer a stroke than those randomized to placebo. Estrogen–progestin was associated with an approximate doubling in risk for pulmonary embolism and deep vein thrombosis, and estrogen alone was associated with a 35%–50% increase in these risks. Both HT regimens led to a significant 10%–15% increase in risk of total cardiovascular events, a composite endpoint that included MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, pulmonary embolism, deep vein thrombosis, and cardiovascular death.

In absolute terms, an estimated additional 19 cardiovascular events, including 6 CHD events, 9 strokes, and 21 venous thromboembolisms (VTEs), would be expected to occur among every 10,000 women assigned to estrogen–progestin for one year, and an estimated additional 27 cardiovascular events, including 3 fewer CHD events, 11 more strokes, and 11 more VTEs, would be expected among every 10,000 women assigned to estrogen alone for one year.

3.2. *Cancer*

Women randomized to estrogen–progestin experienced a significant 24% increase in the risk of breast cancer compared with those randomized to placebo. In contrast, randomization to estrogen alone was unexpectedly associated with a risk reduction of 21% that approached statistical significance. Biologic explanations for the latter finding remain elusive [11]. Assignment to estrogen–progestin was associated with a significant risk reduction of 38% for colorectal cancer and a nonsignificant 17% reduction in endometrial cancer, respectively, whereas assignment to estrogen alone was unrelated to risk of these cancers. Neither estrogen–progestin nor estrogen alone was associated with risk of total cancer.

The absolute risks of specific cancers per 10,000 women per year in the HT groups compared with placebo groups are shown in Table 1. Considering all cancer types, there would be 4 excess cancer cases per 10,000 women per year using estrogen–progestin. In contrast, with estrogen alone, there would be 8 *fewer* cancers of all types per 10,000 women per year.

3.3. *Other Endpoints*

Significant reductions in risk of hip fracture, type 2 diabetes, and gallbladder disease were observed with both HT regimens. Estrogen–progestin doubled the risk of probable dementia (this outcome was assessed only in women aged ≥65), and estrogen alone led to a 47% increase in risk. Estrogen–progestin also appeared to increase ovarian cancer risk (relative risk [RR] = 1.41, 95% confidence interval [0.75–2.66]), but the estimate was imprecise because of the small number of cases. Neither estrogen–progestin nor estrogen alone was associated with total mortality. WHI investigators created a