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The risk of fatal stroke in Finnish postmenopausal hormone therapy users before and after the Women's Health Initiative: A cohort study

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ABSTRACT

Objective: The Women's Health Initiative (WHI) study clarified the indications and contraindications for postmenopausal hormone therapy (HT). We studied the impact of the WHI results on the risk of fatal stroke in HT users in Finland.
Study design: Retrospective analysis setting: Nationwide registers on postmenopausal HT use and causes of death between 1995 and 2009.
Population: Women ≥40 years (n = 290,272) using systemic estradiol-based postmenopausal HT.
Methods: Follow-up started from the first HT purchase during the pre-WHI era (1995–2001) and post-WHI era (2002–2009).
Main outcome measures: Stroke deaths in HT users were compared with that in the age-matched background population and expressed as standardized mortality ratio (SMR) with 95% confidence intervals.
Results: Overall, 311 HT users died due to stroke. The exposure to HT ≤1 year was associated with a similarly reduced 22% (0.67–0.91) risk of stroke death in the pre-WHI era and in the post-WHI era 27% (0.55–0.94). The risk reductions for HT exposure of 1–8 years in the pre-WHI era (47%, 0.42–0.65) did not differ from that in the post-WHI era (32%, 0.48–0.94). The discontinuation of HT was accompanied by a significant 33% (1.02–1.72) increase in stroke death risk in the pre-WHI era and a non-significant 32% (0.84–1.99) increase in the post-WHI era within the first post-treatment year, but no longer after 1–8 years.
Conclusions: The change in prescribing policy after the WHI study did not affect the risk of fatal stroke in Finnish HT users.

1. Introduction

Stroke is the third most common cause of death and the most common cause of prolonged disability in women worldwide [1]. Therefore, the American Heart and Stroke Association recently published strict new guidelines for the prevention of stroke in women [2]. These guidelines acknowledge a number of female gender-related risk factors for stroke, such as migraine, pregnancy, pre-eclampsia, atrial fibrillation, obesity, metabolic syndrome, living alone status and consequent delay in thrombolysis, and longevity. With regard to female sex hormones, the impact of contraceptive steroids as a risk factor for stroke is more strongly established [2] than that of postmenopausal hormone therapy (HT) [3].

Postmenopausal hormone therapy is still the most effective treatment for menopausal symptoms, which are present in up to 80% of women at menopausal age [4]. In addition to effective symptom relief, HT may affect vasculature. Observational studies have shown a decreased [5] or increased [6] risk of stroke in users of systemic HT. In the first randomized HT trial, the Women's Health Initiative study (WHI), the combination of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) was associated with a 50% elevation in the risk of stroke in women who had initiated HT at 60–69 years of age [7,8]. The risk of stroke was also increased age-dependently in women who had a history of myocardial infarction [9]. When the data of four randomized HT trials

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comprising 15,423 women with HT and 14,582 control women were meta-analyzed, a significant 15% elevation in the risk of stroke in past and current users of HT was seen; this risk vanished after the discontinuation of HT [10]. The picture is not fully clear, and indeed, in one placebo-controlled study, HT proved to be safe even in women with previous ischemic stroke [11]. The vast majority of preceding data have been collected from women using CEE alone or CEE plus MPA. Therefore, it is of interest that estradiol alone or in combination with MPA was significantly safer than CEE, as it regards the risk for stroke [12].

In Finland, the risk of occlusive vascular disorders is among the highest in Europe [13]. Therefore, in the 1980s and 1990s, according to uniform international guidelines for optimal HT use [14,15], HT was specifically recommended for the primary prevention of stroke and other vascular disorders also in Finland. Results of the WHI study published in 2002 [7] rapidly discontinued such a prophylactic HT prescribing and also otherwise scrutinized the indications for HT use. We recently reported [16] that the WHI study induced changes in indications and contraindications for the initiation of HT failed to affect the risk of coronary heart disease mortality, the leading killer in Finland [17]. These findings inspired us to analyze if the WHI study brought along detectable changes in the risk of fatal stroke among HT users.

2. Methods

All Finnish women buying HT regimens, available only with a doctor's prescription, have been entered into the nationwide reimbursement (42–50% of HT price reimbursed) register since January 1st, 1994. For this study we considered users of systemic HT who were ≥40 years at the first purchase of HT. Women younger than 40 years (n = 63,189), those purchasing only progestins (n = 47,492) or vaginal estrogen therapies (n = 195,756) were excluded. Because we could not be certain if the HT purchase in the register opening year 1994 was really the first one or whether a HT buyer was continuing a HT regimen started before the register opening, we decided to include only the women whose first HT purchase was entered into the register in 1995 or later ("new starters").

In contrast to the US where CEE is favored, 99.6% of HT regimens used in Finland contain estradiol. Hysterectomized women are allowed to use estradiol-only regimens (ET), whereas the others complement ET with 10–14 days of progestin courses each month (sequential EPT regimen) or each day (continuous EPT) for endometrial safety. Estradiol alone or in combination with a progestin could have been used orally or transdermally as a gel or a patch. Hormone regimens, traced with trade names, were translated into generic hormones and classified according to the mode of administration (oral, transdermal), or to the type of the regimen (ET, sequential EPT, and continuous EPT; the latter also included users of tibolone). Some women formed individual EPT regimens by combining estradiol with individual progestin courses at 1–3 month intervals; they were considered as EPT users. Women may have switched between different regimens, and thus, cumulative exposure day for each HT regimen were calculated for every woman. Discontinuation of treatment was identified as no further purchases in six months after the preceding purchase. Women with CEE use (n = 1305, 0.4%) were included into ET use and women with tibolone (available from 2000 onwards) (n = 30,255) were included into the continuous EPT group. Because systemic HT use results in substantially higher elevations in the circulating levels of estrogens than a vaginal regimen does, the possible use of vaginal estrogens in addition to systemic HT was not considered as a confounding factor.

In Finland, all deaths are recorded in the Causes of Death Register. Reporting to this register is mandatory and done by physicians. The register is accurate since the causes of death are checked by physicians at regional and national level [18]. From this register, we identified all deaths due to stroke (ICD-9: 430–438 in 1995 and ICD-10: I60–I69 since 1996) in women aged ≥40 between 1995 and 2009. Ischemia is the most common cause for stroke (~80%), which is the type stroke that has been associated with HT. Less common causes for stroke include intracerebral or subarachnoidal hemorrhage [19,20]. In this study we could not differentiate between these subtypes.

Because the WHI study published in 2002 brought along drastic changes in Finnish prescription practice, we defined the pre-WHI era as 1995–2001 and the post-WHI era as 2002–2009. Thus, the follow-up time could maximally be seven years for women included in the pre-WHI era series, and eight years in the post-WHI series. The follow-up started from the first purchase of HT (at its earliest on January 1st, 1995) and ended on December 31st, 2009 or at death, and the woman-years followed up were calculated for various types of HT use. We classified the exposure times to HT as ≤1 year to whether HT brought along immediate stroke deaths, and >1 to 8 years, which was the maximal follow-up time within our study. The same follow-up periods were also employed for the follow-up times since the discontinuation of HT.

The number of stroke deaths in HT users was compared to the expected number of deaths due to stroke in the age- and year-matched background population (also including HT users) by a standardized mortality ratio (SMR with 95% confidence intervals (CI) following the Poisson model. Due to the small numbers of events in the pre- and post-WHI eras, we could not analyze the possible differences in the risk of fatal stroke in users of oral or transdermal estradiol, or the impact of different estradiol doses.

Before the initiation of the study, the research committee at the Helsinki University Central Hospital approved the study, Thereafter, appropriate approvals to use the confidential register data in scientific research were obtained from the following authorities: (1) the National Institute for Health and Welfare (THL/1370/5.05.00/2010), (2) Statistics Finland (TK-53-1560-10), and (3) Social Insurance Institution of Finland (KELA 40/522/2010).

3. Results

During the entire study period of 1995–2009 a total of 290,272 women used HT with an average exposure time of 4.0 ± 3.4 (mean ± standard deviation) years. Among women with exposure to HT >1 year (mean ± standard deviation), the exposure time to HT was 5.2 ± 3.1 years. The prevalence of HT users in women ≥50 years fell from 25% in 2001 to 15% in 2009 evidently in response to the WHI study. There occurred 231 stroke deaths in the pre-WHI era and 80 stroke deaths in the post-WHI era.

The use of any systemic HT, or of ET or EPT separately, were accompanied by reductions in stroke mortality, which did not differ significantly between the pre-and post-WHI eras (Table 1). The risk reductions were evident already with ≤1 year exposure, and the risk of death due to stroke decreased further when exposure to any HT was prolonged to 1–8 years. When stratified by age during HT use, the risk reductions with ≤1 year exposure to any HT in the pre- and post-WHI eras were no longer significant, probably due to the small number of events (Table 2). A prolonged HT exposure of 1–8 years in the pre-WHI era was accompanied by reductions in the risk of fatal stroke in women aged 50 or more. In the post-WHI era, the same exposure times were associated with reduced risk of death due to stroke only in women aged 50–59. In the pre- and post-WHI eras, the exposure years to HT collected under or at 60 years were accompanied with comparable risk decreases as HT exposure years collected over 60 years of age (Table 3). No statistically significant differences emerged between the pre-and post-WHI eras. In the