Increased cardiovascular mortality risk in women discontinuing postmenopausal hormone therapy

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Context: Current guidelines recommend annual discontinuation of postmenopausal hormone therapy (HT) to evaluate whether a woman could manage without the treatment. The impact of HT on cardiovascular health has been widely studied, but it is not known how withdrawal of HT affects cardiovascular risk.

Objective: We evaluated the risk of cardiac or stroke death after the discontinuation of HT.

Design, Patients, Interventions and Main Outcome Measures: Altogether 332 202 Finnish women discontinuing HT between 1994–2009 (data from National Reimbursement register) were followed from the discontinuation date to death due to cardiac cause (n=1 177) or stroke (n=1 952), or to the end of 2009. The deaths, retrieved from the national Cause of Death Register, were compared with the expected number of deaths in the age-standardized background population. In a sub-analysis we also compared HT stoppers with HT users.

Results: Within the first post-treatment year, the risk of cardiac death was significantly elevated (standardized mortality ratio; 95% confidence interval 1.26; 1.16–1.37), whereas follow-up >1 year was accompanied with reduction (0.75; 0.72–0.78). The risk of stroke death in the first post-treatment year was increased (1.63; 1.47–1.79), but follow-up >1 year accompanied with a reduced risk (0.89; 0.85–0.94). The cardiac (2.30; 2.12–2.50) and stroke (2.52; 2.28–2.77) death risk elevations were even higher when compared to HT users. In women who discontinued HT at <60, but not in women aged ≥60 years, cardiac mortality risk was elevated (1.94; 1.51–2.48).

Conclusions: Increased cardiovascular death risks question the safety of annual HT discontinuation practice to evaluate whether a woman could manage without HT.

A wealth of epidemiological data exists indicating the beneficial effect of postmenopausal hormone therapy (HT) on cardiovascular health (1, 2). However, these findings were not confirmed in placebo-controlled trials, like in the HERS (3) and in the WHI (4). Furthermore, an increased risk of cardiovascular events has been associated with HT initiation, particularly in the secondary prevention trials, (3) although after a myocardial infarction (MI) the continuation of HT did not increase the risk of reinfarction (5). Thus, the current guidelines recommend that HT should be used only in recently menopausal women for moderate-to-severe vasomotor symptoms for the shortest possible time (6). Moreover, annual HT discontinuation, either immediately or tapered, (7) has become a routine practice to evaluate if a woman could manage without HT.

Abbreviations:
Estrogen has direct cardiovascular effects (8). These effects are regulated by the genomic action of estrogen receptors, (9) that activates the release of vasodilatory agents, such as nitric oxide and prostacyclin. At the same time, the release of endothelin-1, the most potent vasoconstrictor, is reduced (9). Thus, vasodilation and blood pressure (BP) are both affected, not only by fluctuations in circulating estrogen levels during the menstrual cycle, but also during estrogen supplementation in controlled animal experiments (10, 11) or in postmenopausal women (12, 13). For instance, in postmenopausal women estradiol dilates coronary arteries within hours (14) and increases cerebral perfusion within minutes (15). Female gender is also an independent risk factor for arrhythmias (16). Furthermore, the onset of perimenopause or meno-pause with fluctuating estrogen levels is associated with a 3–8-fold increase in the risk of fatal or potentially fatal cardiac events in women with a specific congenital long-QT syndrome, (17) which is the most common inherited arrhythmogenic disorder without structural heart disease (18).

No large-scale epidemiological studies on the cardiovascular effects of HT discontinuation exist, although in view of the rapid vascular responses with estrogen, such an effect is possible. We report here the risk of cardiac or stroke death after the discontinuation of HT use using data from a nationwide study.

Materials and Methods

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).

Altogether 332 202 women discontinued the use of HT in Finland between the years 1994–2009. This population was traced from the nationwide reimbursement register into which each woman who buys HT is entered. A part of the HT price (40%–60%) is reimbursed, and such a therapy is available only with a doctor’s prescription. The patient must visit the pharmacy at three months intervals to get her HT regimens; each of these visits is entered into the register. Thus, a woman failing to purchase additional HT regimens was judged to have discontinued her HT regimen. The date of discontinuation was defined as the date of the last HT purchase plus six months. Therefore, the last eligible date for a purchase was June, 30th, 2009.

These women aged ≥ 40 years were followed from the date of the HT discontinuation to death, or to the last day of 2009 with the aid of National Cause of Death Register. This register, which is mandated by law to collect all deaths in Finland, has been proven to be accurate (19). It is noteworthy that if the cause of death is not obvious based on premortal findings, autopsies are carried out in approximately 30% of cases. The expected numbers of cardiac or stroke deaths were placed in 5-year-age groups with approximation based on the statistics of the entire country. The number of woman-years in each 5-year age group was multiplied by respective rates for cardiac and stroke deaths during the same observation period. The numbers of observed cardiac and stroke deaths were divided by the respective expected numbers (standardized mortality ratio [SMR]). The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the numbers of observed cases (20). Cardiac and stroke deaths were also compared between HT stoppers and users (21).

The follow-up time was divided into the first post-treatment year, likely to collect HT discontinuation-related changes in mortality, or from one year onwards. The follow-up time was also separately assessed for women exposed ≤ 5 or > 5 years to HT. Because the actual use of HT may cause vascular benefits, if initiated under 60 years of age, but vascular hazards, if initiated over 60 years of age (“window theory”), (22) we separately compared the death risks in women who had been under or over 60 years when they initiated or discontinued the HT.

The preceding HT use could be estradiol-only with a possible simultaneous use of a levonorgestrel-releasing intrauterine device (IUD). Such a device does not cause clinically meaningful circulating levels of levonorgestrel (23). The nonhysterectomized women had used, in addition to estradiol, various progestins of which the most common had been norethisterone acetate (44%), followed by medroxyprogesterone acetate (27%), dydrogesterone (12%) and others (17%) (24). The progestin component could be given sequentially when a progestin component was added to estradiol for 10–14 days at each month or at three months intervals, or to users of continuous estradiol plus progestin when progestin was given every day concomitantly with estradiol. Because estradiol is the primary mediator for HT effects, we decided to make no distinction between estradiol-only users and users of various estradiol plus progestin regimens in this study. A possible use of vaginal estrogens, which are also available over the counter, was not considered as a confounding factor.

Results

The number of women discontinuing HT gradually decreased since 1994 (Figure 1). Altogether, 332 202 women who discontinued their HT could be followed for 1.97 million years, and in total 5129 cardiac or stroke deaths were encountered (Table 1). As a mean, these women had been exposed to HT for 6.2 ± 6.0 (SD) years. The mean follow-up time was after discontinuation was 5.5 ± 3.8 (SD) years.

Within the first post-HT year, the risk of any cause mortality was significantly increased (SMR 2.28; CI 2.23–2.34, P < .05). This risk elevation vanished when the follow-up was prolonged over one year (1.00; 0.99–1.02). Within the first follow-up year, the risk of cardiac death was significantly elevated (1.26; 1.16–1.37, P < .05) regardless if HT exposure was below or over 5 years (Table
The prolongation of the follow-up over one year was accompanied with significant reductions in the cardiac SMR and this was also seen when all HT stoppers were evaluated regardless of the time since last HT (Table 2).

Within the first follow-up year, the stroke mortality risk was elevated (1.63; 1.47–1.79, \(P < .05\)) (Table 2). The extension of the follow-up over one year was associated with significant reduction (11%) in SMR for stroke. These changes in the stroke SMR were not related to the duration of the preceding HT exposure, and when all HT stoppers were evaluated regardless of the time since last HT the stroke death risk did not differ (Table 2).

In women who had initiated HT < 60, but not in women \(\geq 60\) years of age, the risk of cardiac death was increased (1.74; 1.37–2.19) within the first post-HT treatment year. This risk remained elevated when the HT exposure had exceeded 5 years (Table 3A). The risk increases for stroke death tended to be even higher, but showed otherwise similar pattern as for cardiac death risk (Table 3A).

In women who had discontinued the use of HT at \(< 60\) years of age the cardiac mortality risk was elevated (1.94; 1.51–2.48) within the first post-HT treatment year. This risk was further increased if the preceding HT exposure had lasted \(\geq 5\) years (Table 3B). The risk increases for stroke mortality appeared higher, but with a similar pattern as for cardiac death risk (Table 3B).

When HT stoppers were compared with HT users, the elevations in SMR for cardiac (2.30; 2.12–2.50) and stroke death (2.52; 2.28–2.77) were significant for the first post-treatment year and thereafter, although the first year risks were higher (Table 4).

### Table 1. Follow-up years and total numbers of deaths due to coronary heart disease and stroke in women discontinuing hormone therapy (HT).

<table>
<thead>
<tr>
<th>Time since last HT use (years)</th>
<th>Total follow-up years</th>
<th>Follow-up years according to HT exposure</th>
<th>Follow-up years according to HT exposure</th>
<th>Deaths due to coronary heart disease</th>
<th>Deaths due to stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\leq 1)</td>
<td>317 711</td>
<td>168 634</td>
<td>149 076</td>
<td>568</td>
<td>387</td>
</tr>
<tr>
<td>(&gt; 1)</td>
<td>1 653 595</td>
<td>1 007 217</td>
<td>646 378</td>
<td>2609</td>
<td>1565</td>
</tr>
<tr>
<td>Total</td>
<td>1 971 306</td>
<td>1 175 851</td>
<td>795 454</td>
<td>3177</td>
<td>1952</td>
</tr>
</tbody>
</table>

Discussion

Cardiovascular deaths account for almost half of the mortality in western women, and the impact of actual HT use on cardiovascular health has been widely studied (1–4, 21). Also extended post-treatment follow-up data up to
6.6 years exist from the WHI (25). Based on the findings from the recent clinical trials and current guidelines, an increasing number of women choose to discontinue HT. However, it is not known how the acute withdrawal of HT may affect cardiovascular risk. Thus, in a nationwide study with almost two million follow-up years, we evaluated the cardiac or stroke mortality risk after discontinuation of HT comparing against age-standardized background population and also against HT users. We detected that particularly the first year after the cessation of HT was accompanied with elevations in the risk for cardiac or stroke death. Moreover, these elevations were markedly higher in women less than 60 years as compared to women over 60 years of age when they discontinued HT treatment. Similar risk pattern was detected also when the women were stratified by age at HT initiation (<60 vs 60 years). These findings propose that withdrawal of HT may have unfavorable cardiovascular effects, particularly in recently menopausal women.

Estrogen has rapid vasodilatory effects both in coronary (14) and carotid (15) arteries mediated by vasodilatory agents, such as nitric oxide and prostacyclin (26). While a short estrogen treatment induces a rapid non-genomic synthesis and release of nitric oxide that occurs within minutes, a longer exposure to estrogen promotes nitric oxide synthase gene expression, leading to a further increase of nitric oxide synthesis (26). Estrogen also inhibits the release of endothelin-1, the most potent vasoconstrictor (8). Therefore, a rather acute estrogen withdrawal, as in discontinuation of HT, may result in constriction of arteries (9, 13, 26). This could endanger adequate coronary circulation eg, in women with unstable

Table 2. Risk of death due to coronary heart disease (CHD) or stroke in women discontinuing postmenopausal hormone therapy (HT).

Table 3. The impact of age <60 or ≥60 yr at hormone therapy (HT) initiation (A) or discontinuation (B) on the risk of cardiac or stroke mortality during the first post-HT treatment year. SMR: standardized mortality ratio. CI: confidence interval.

Table 4. Cardiac or stroke death risk in women discontinuing postmenopausal hormone therapy (HT) when compared to HT users.

SMR: standardized mortality ratio. CI: confidence interval

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angina or for cerebral circulation eg, in women with calcified carotid arteries and a possible tendency to transient ischemic attacks. These changes may result in potentially fatal MI or stroke.

Menopause (27) and menopausal vasomotor hot flushes (28) are associated with increased sympathetic and decreased parasympathetic activity that may enhance the risk of cardiovascular events (29). Women with vasomotor hot flushes also frequently report palpitations or arrhythmias (30). Furthermore, women with congenital long-QT syndrome have a 3–8-fold increased risk of arrhythmias, syncope and sudden cardiac death due to hormonal fluctuations both at menopausal transition and in actual menopause (17). Since HT prevents vasomotor hot flushes and also palpitations, HT withdrawal could predispose some women to fatal arrhythmias. In our study the higher risk for death in recently menopausal women as compared to elderly women may imply a higher sensitivity of arteries and heart towards estrogen in younger women, a feature that may have been reduced or lost in elderly women (8, 9). Thus, our post-treatment data support the “window theory”, suggesting that actual HT use may be protective against vascular events in younger but not in older women (30).

Myocardial infarction is fatal immediately or within the first month in approximately one third of the female patients, (32) whereas ischemic stroke kills about 10%–20% of patients during the first 90 days; 80% of stroke cases are ischemic in origin in Finland (33). According to our current guidelines, HT use should be discontinued after MI or stroke, although this was not generally the case prior to the Women’s Health Initiative publication in 2002 (5). We have no data on whether women continued or discontinued HT in this study after a nonfatal MI or stroke, but in another Nordic study, 80% of women continued the use of HT after a MI (33). We studied cardiac and stroke deaths in the present study and thus, the women who discontinued HT use after MI or stroke but survived were not included into our series. Of patients surviving the first three months after vascular attacks, half will die after MI (34) and 25% die after stroke within the first year. Thus, these deaths may have been accumulated and perhaps partly explain the excess deaths within the first follow-up year. These risk rises largely contributed also to the increase in any cause mortality risk.

The short-term case fatality and incidence of recurrent cardiovascular events in women are higher than those in men (35) and this difference has been traditionally explained with older age and a higher prevalence of risk factors among elderly women. However, more recent studies indicate that younger women (<55 years) are characterized with a higher in-hospital death rate (36) and poorer improvements in prognosis (32) compared to older women. Reasons for this phenomenon are not known, but in addition to atypical symptoms and suboptimal treatment, (37) hormonal factors, including changes in HT use, may well have a role.

Our study has several limitations. First, with observational setting we cannot exclude a “healthy woman”-bias that could partly explain the cardiovascular risk reductions with the prolongation of the follow-up. Against this criticism speaks the liberal HT prescription policy in the pre-WHI era when women with vascular risk factors were encouraged to start the use of HT for vascular protection. Second, no data existed for the dates of MI or stroke, and the discontinuation date of HT could harbor maximally a 3 months error. Third, we lack data for confounding factors, such as smoking, weight, BP, cholesterol levels or family risk for these conditions. Moreover, we did not know if women discontinued HT use suddenly or gradually; this could potentially relate to the cardiovascular death risk. Finally, we compared HT users with the age-standardized background population, also including HT users. Thus, the HT effects, positive or negative, were slightly diluted in our study. It is noteworthy that we also compared the death risks in women discontinuing HT with HT users. The death risks in this comparison were enlarged, perhaps expectedly due to the significant risk reductions of cardiac and stroke mortality seen in HT users (21).

Our study has also several strengths. In this nationwide study with 15 years follow-up we were able to analyze a large number of women who discontinued HT. Moreover, we are convinced that data for the preceding HT and for the discontinuation dates are accurate and often verified in previous studies (21, 38). We would also like to emphasize that if the diagnosis of cardiovascular death was disputable, an autopsy took place (19). Thus, the causes of death register, mandated by law and run by the state, is reliable. Furthermore, health care in Finland is almost free of charge, and thus, there is hardly any bias in the access to medical care between the previous HT users and the background population. It is also noteworthy that the Finnish HT users do not differ in a socioeconomic aspect from the nonusers (39).

In the first post-treatment year the discontinuation of HT use was accompanied with 26%–66% elevations in the risk for cardiac or stroke death. This risk elevation was markedly higher in women who were younger than 60 years at the initiation or discontinuation of HT use. Although the risk for cardiovascular deaths were not enhanced when analyzed regardless of the time since last HT we may, however, calculate that overall the discontinuation of HT of any duration could potentially be related...
with 4 extra cardiac deaths and 5 stroke deaths in 10 000 women within the first post-treatment year. Our findings question the safety of annual discontinuation practice to evaluate whether a woman could manage without HT. Our data also warrant further studies to compare the cardiovascular safety of immediate vs tapered HT discontinuation.

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References


